

**Probabilistic information and decision  
making in the health context.  
The package leaflet as a basis for informed  
consent.**

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*I dedicate this work to my parents Marisa and Mario,  
to my brother Walter and his family,  
and to all my friends on earth and in heaven,  
especially to Gavin Boyd  
and Father Pancrazio Gaudio*



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## **Abstract**

Package leaflets (PL) belong to the complex communication system related to the minimization and prevention of pharmaceutical risk. Their legal nature is not exhausted by safety regulation though: as a privileged form of product instruction, they are also subject to liability regulation with a consequent reallocation of damage responsibility through risk disclosure. After illustrating the articulation of pharmaceutical risk through risk prevention norms (residual risk, development risk), the thesis goes on with a discussion of the PL role within the therapeutic decision as a complementary vehicle to doctor's information. It results that the liability framework in which both information channels are embedded determines a communication model, which far from promoting a shared decision process, radicalizes the two-step communication structure typical of the informed consent model inherited by surgery judicature.

The second part investigates PL information as a source of knowledge updating through the methodological tools provided by Bayesian decision theory.

Finally, an empirical study conducted over a sample of 55 drug consumers investigates the impact of PL information on drug risk perception and its perceived value to therapeutic decision.

## Acknowledgments

This dissertation is the fruit of three academic environments: Lugano, Mainz, and Bielefeld. It therefore enjoys the integration of different research approaches and mentalities. However this state of affairs is rather the consequence than the source of the multidisciplinary approach adopted for this research. In fact the social relevance of the topic at issue, the complex legal, scientific, ethical framework in which it is embedded, and not ultimately the conflicts of interests which affect it, are at the origin of this multifaceted work.

I thank the very idea of tackling this theme to Prof. Peter Schulz of the Institute of Communication and Health at the University of Lugano. It is within the framework of my collaboration to a research project on antibiotic resistance (FNR 49) in the ICH, that the role of package leaflets in therapeutic compliance was identified as a decisive factor in antibiotic health literacy. The analysis of package leaflets was part of a more complex investigation design, where consumer's information about antibiotics should be examined in relation to different sources and media (the doctor, the press). The multidimensional approach of this project has given me an overview of the communication flux around the consumer and about the pharmaceutical. This has raised the awareness that more comprehensive research results would have been produced by investigating the role of PL within the entire communication context in which it is embedded.

Together with my supervisor, Prof. Eddo Rigotti – Institute of Semiotics and Linguistics – this insight has been further articulated in the *fil rouge* which underlies the entire work: the comparison between the legislator's model of PL function within pharmaceutical regulation, and the approach of drug consumers to the PL text. The complexity of the aspects involved would have led me astray, had not my supervisor constantly encouraged me and helped me keep the line of the argumentation. I heartily thank him for his patience and guidance.

I take the opportunity to thank also Prof. Marco Colombetti, to whom I owe fruitful insights as to the nature of the communicative act presupposed by PL risk disclosure (see chapter 4): the analysis of institutional communication proposed by him and his colleagues have provided the theoretical framework which has allowed the integration of legal and communicative considerations about the multiple PL functions and institutional effects.

In Mainz I could advantageously profit from the risk communication seminar held by Dr. Simone Ehmig of the institute of Publizistik at the Gutenberg University. The topics addressed in the course – lay risk perception and probabilistic reasoning –

have introduced me into the theme of expert-to-lay communication in the risk context, and especially in the discrepancy between expert and lay risk perception. I thank also Prof. Dr. Hans Keplinger, director of the same institute, for the precious advices which he has offered me on the basis of his long experience with content analysis of package leaflets and mass communication in general.

The longer stay in Bielefeld has significantly influenced my research. First of all, I due to Prof. Strohner (Fakultät für Linguistik und Literaturwissenschaft) the empirical approach to the topic. Also the think-aloud experiment is part of a series of methodological advices, which I could profit from thanks to his support and supervision. The questionnaire was edited with the help of Prof. Dr. Wulf Albers (Fakultät für Mathematik und Wirtschaftswissenschaften): I thank him for the interest expressed in the topic and for dedicating much of his precious time in the examination of the most suited linguistic format and layout.

I also would like to thank Kjell Hoffmann for his kind support in the exploratory analysis of the questionnaire data.

Dulcis in fundo, I wish to express my gratitude to Prof. Dr. Elizabeth Gülich. She was a reference point during all my stay in Bielefeld in many respects. Her continuous and solicitous feedback helped me overcome many research impasses found along the way to the destination. More importantly, her open-mindedness and analytical insight have both encouraged me to undertake unknown paths and prompted me to stick to the point of research at the same time. For many reasons I also owe to her my endurance.



# Introduction

Pharmaceutical products are at the centre of vivacious debates, and the importance of transparent, timely and comprehensive information is acknowledged by the society at large as an indispensable means of risk prevention and consumers' protection.

The relevance of timely information for an effective risk management has particularly come to light in the occasion of sadly famous pharmaceutical scandals such as the Contergan tragedy in Germany, up to the recent Vioxx case in the U.S.<sup>1</sup> Precisely as a consequence of the Contergan scandal, in Europe, and particularly in Germany, a detailed regulation of pharmaceutical risk management and information has been developed and continues to absorb legal theorists and policy makers in the complex task of conciliating the widest possible accessibility to health technology innovations with the requirement of safety.<sup>2</sup>

Debates about pharmaceutical products focus on one and the same concern: Health as an individual and societal good, which drugs contribute to promote and threaten at the same time.

The need for preventing damaging events has led to a strict regulation of the pharmaceutical market. Pharmaceutical risk communication is at the core of this regulatory activity and aims at protecting *health and life* as constitutional goods regarding both the individual and the society, but also the right to an *autonomous therapeutic choice* by patients with regards to the benefits and risks associated with any pharmaceutical product.

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<sup>1</sup> For a recent discussion see: Gaßner, Reich-Malter, 2006: 147 ff.

<sup>2</sup> European directives on pharmaceuticals have been issued since 1965 with the council directive [65/65/EEC \(Official Journal 22, 9.2. 1965, p. 369/65, amended through directives 66/454/EEC, 75/319/EEC, 83/570/EEC, 87/21/EEC, 89/341/EEC, 92/27/EEC, 93/39/EEC\)](#); following to the first directive other council directives with related amendments have been issued: [75/318/EEC \(amended through 83/570/EEC, 87/19/EEC, 89/341/EEC, 91/507/EEC, 93/39/EEC, 1999/82/EC and 1999/83/EC – commission directives\)](#); [75/319/EEC \(amended through 78/420/EEC, 83/570/EEC, 89/341/EEC, 92/27/EEC, 93/39/EEC, 2000/38/EC – commission directive\)](#); both directives can be considered as the legislator's answer to the Contergan catastrophe; finally directives [89/342/EEC, 89/343/EEC, 89/381/EEC, 92/25/EEC, 92/26/EEC, 92/27/EEC, 92/28/EEC, 92/73/EEC](#), the most recent commission directive assembles all preceding ones in a single text: [2001/83/EC \(amended through 2002/98/EC, 2003/63/EC, 2004/24/EC, and 2004/27/EC\)](#).  
The German legislation has evolved from a mere danger avoidance to a risk prevention system through the German Medicines Act issued in 1976 (Gesetz über den Verkehr mit Arzneimitteln: Arzneimittelgesetz – AMG). This law has evolved in accordance to European legislation and in the attempt to meet the safety requirements deriving from the continuously evolving pharmaceutical field. Amendments to AMG 1976 have been issued in 1983 (1<sup>st</sup> amendment), 1986 (2<sup>nd</sup>), 1988 (3<sup>rd</sup>), 1990 (4<sup>th</sup> and 5<sup>th</sup>), 1996 (6<sup>th</sup>), 1998 (7<sup>th</sup> and 8<sup>th</sup>), 1999 (9<sup>th</sup>), 2000 (10<sup>th</sup>), 2002 (11<sup>th</sup>), 2004 (14<sup>th</sup>), 2005 (13<sup>th</sup>, 14<sup>th</sup>, 15<sup>th</sup>).

As a special support of such sort of information, the drug package leaflet has been object of thorough legal regulation, which has been amended and refined through the time by the legislator.<sup>3</sup>

In despite of these efforts, the package leaflet is still object of harsh criticism and is blamed by health professionals of hindering compliance and failing to provide a valid information support for therapeutic decision.<sup>4</sup> Moreover, in Germany, recent court decisions concerning damage compensation for information faults have delivered contradictory judgments in relation to package leaflet information:

- A much discussed sentence of the LG Dortmund (6. 10. 1999)<sup>5</sup> has emphasized the patient's responsibility in taking notice of the risks reported by the package leaflet as a basis for his own risk/benefit evaluation and consequent therapeutic decision.
- In contrast to this sentence, other decisions,<sup>6</sup> have pointed at the inadequacy of this information support alone – and generally of standardized forms of risk disclosure (brochures, pre-drafted formularies) – as a sufficient source of therapeutic information for the lay consumer: in these sentences, doctor's personal and tailored communication is considered a necessary condition for consent to be valid, and cannot be substituted by PL information.

The legal debate concerns the distribution of risk responsibility among patient, doctor, and pharmaceutical firm in relation to the delivered information.

In fact, differently than in the U.S, where no legal value is assigned to pharmaceutical product instruction, and the theory of “learned intermediary” imposes information duties only on the doctor, PL information has in Germany, a

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<sup>3</sup> In particular, the European guideline 92/27/EEC recommends the insertion of product instructions in the drug package specifically addressing the patient. The 92/27/CEE directive (31. 3. 1992) represents a milestone in the development of pharmaceutical labeling. It provides a detailed list of information contents that the PL text must cover (particularly at point 3 of art. 7 and in art. 8) and invites to a closer connection with the layman medical background (the notion of “health literacy” is explicitly mentioned). In 1998 “A Guideline on the readability of the Label and Package Leaflet of Medicinal Products for Human Use” has been emanated as a valid companion to an enhanced patient information quality. The document presents a set of examples and provides a guideline for testing PL readability. The 1992 directive with related guideline have been officially implemented in the German legislation in 2002, through the recommendations for the configuration of package leaflet, and translated in legal norms through the 14<sup>th</sup> amendment to AMG. More recently, § 61 I of the modified European directive 2001/83/EC prescribes the introduction of a comprehensibility test for patient leaflets as part of the documentation for drug approval. This requirement has been implemented in the German Law through § 22 VII, 2 AMG in the 14<sup>th</sup> AMG-amendment, which declares: “Der zuständigen Bundesbehörde sind bei Arzneimitteln, die zur Anwendung bei Menschen bestimmt sind, außerdem die Ergebnisse von Bewertungen der Packungsbeilage vorzulegen, die in Zusammenarbeit mit Patienten-Zielgruppen durchgeführt wurden.”

<sup>4</sup> See among others Aumiller, 1978, 1982; Degner, 1982, Karpa, 1991, Kepplinger 1990, 1991, Nickolaus, 1991; Nöthlich, 1991; Wenzel, 1985; Winckelmann, 1983; Wolff, 1982; Zink, 1985; Zylka, 1986. Until recently the BfArM (Bundesinstitut für Arzneimittel und Medizinprodukte – the German Federal Office for Drugs and Medical Products – has organized a seminar for investigating the state of the art as for PLs readability and patient friendliness.

[http://www.bfarm.de/cln\\_042/nr\\_599148/DE/BfArM/Publikationen/Praesentationen/060215-Dialog.html](http://www.bfarm.de/cln_042/nr_599148/DE/BfArM/Publikationen/Praesentationen/060215-Dialog.html)  
Bonn, 15.3.2006.

<sup>5</sup> LG Dortmund, MedR 2000, 332.

<sup>6</sup> BGH, 14. 3. 2006 (NJW 2006: 2108); BGH 15. 3. 2005, NJW 2005, 1716 (1718); BGH 15. 2. 2000 (NJW 2000, 1784).

specific binding force for the drug consumer, which is nevertheless difficult to define precisely because of the information duties also imposed on the doctor.

The issues tackled by this thesis are therefore the following:

- 1) Specify the legal nature of package leaflets on the basis of available juridical sources (statutory law and case law) within the German regulatory system and with respect to prescription drugs;
- 2) Evaluate whether the PL informative-communicative structure allows the patient to accomplish the task(s) established at legal level.

The adoption of these themes in the perspective of communication sciences has been determined by the persuasion that only the integration of the communicative and legal perspectives would lead to the solution of the legal dilemmas raised by PL information.

In fact, the state of the art on the topic presents contributions from the health communication, from the linguistics, and from the legal literature, each of which brings some autonomous advancement in the investigation, whose progress nevertheless seems to be compromised by their reciprocal isolation. This for the following reasons:

- The legal literature cannot claim to exhaustively deal with the complexity of factors involved in the question of drug-consumer information (health risk perception, health information processing, lay decision autonomy) without involving the expertise of related disciplines.
- Linguistic literature cannot clearly grasp the textual typology of the package leaflet – and therefore analyze its congruity to the communicative functions established by the law – without being aware of its contextual functions within the health system.
- Finally, both legal and linguistic literature cannot disregard the insights on lay risk perception and health information seeking behavior gained by psychosociological approaches in the health sciences.

The methodological tool used to integrate the legal and communicative perspectives has been offered by speech act theory. This has helped define the communicative functions of PL information within the German legal system by analyzing its contribution in the determination of the stakeholders' responsibilities (in speech act terms: commitment manipulation).

The analysis of the legal sources brings to the conclusion that PL information has a twofold function:

- 1) consumer safety protection;
- 2) warranty of the consumer's right to self-determination and autonomous decision (in analogy to the institute of informed consent for the doctor-to-patient interaction), with consequent reallocation of risk responsibility.

These two legal tasks translate into two communicative functions:

- 1) risk warning (recommend a behavior which possibly averts so called "avoidable risk");

- 2) risk declaration and consequent disclaiming function (for risk which are considered unavoidably associated to drug consumptions: “residual risk”)<sup>7</sup>.

The evaluative part of the study examines the legitimacy of considering PL information has a legally binding source of information for the drug consumer.

The evaluation is carried out at two distinct levels: a theoretical and an empirical one.

The theoretical evaluation departs from the achievements obtained by linguistic studies. In these studies PL information is blamed to make the reader insecure, and major sources of uncertainty are identified in incomprehensibility, technical language and general reader-unfriendliness.

However, the linguistic approach fails to consider the epistemological uncertainty bound to any decision which is made on the basis of inconclusive knowledge. This is that sort of uncertainty which traces back to insufficient knowledge about the state of affairs related to the decision and the possible outcomes, and which is not removed through reader-friendliness and enhanced comprehensibility.

In order to analyze this aspect of the lay therapeutic decision and the role of PL information within it, a Bayesian approach has been adopted in order to establish the specific epistemic contribution brought by PL information with respect to its legal-communicative functions.

This methodological choice is justified by the fact that Bayesian theory is the privileged discipline in order to account for decision making under uncertainty.

In fact all main components of Bayesian theory (the theory of knowledge updating through probabilistic induction – Bayesian theorem – the theory of decision optimization through maximization of the expected utility; and the theory of information value) are relevant to our research.

In this specific framework, this approach has provided the instruments for analyzing PL information:

- as a basis for knowledge updating (probability of side effects occurrence) for a risk/benefit assessment about the drug;
- as a support for decision optimization based on the expected reward of taking the drug vs. not taking it;
- finally, its perceived value as a function of its expected contribution to decision optimization.

At an empirical level, a quantitative and a qualitative study have been conducted in order to assess how real drug consumers make use of their information in the therapeutic context.

The thesis is subdivided in three parts:

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<sup>7</sup> See later on in the presentation of the single chapters for the distinction between avoidable/intolerable/unacceptable risk and unavoidable/tolerable/acceptable (“residual”) risk.

- I. The first part is devoted to the description of pharmaceutical law in Germany with a focus on the regulation of information exchange among the different stakeholders;
- II. The second part is devoted to the normative analysis of PL information within the context of lay therapeutic choice.
- III. The third part presents some empirical findings derived from a quantitative study and a qualitative research conducted with a sample of subjects that were under therapy at the time of the survey. The purpose of this part is to give a deeper insight on the way drug consumer process PL information and use it in the therapy context.

## **Part I**

### **Pharmaceutical regulation**

The first part of the study is devoted to the pharmaceutical regulation in Germany. Special attention is devoted to norms addressing information exchange among the different stakeholders.

#### **Chapter 1**

An introductory chapter is devoted to pharmaceutical risk management and the distinction between avoidable and unavoidable (residual) risk.

A risk can be avoidable in two senses:

- either because it can be averted by taking adequate precautions,
- or because the risk is unacceptable along risk/benefit considerations.

In this second sense, the underlying principle is that risks are tolerable insofar as they are not avoidable for achieving a certain therapeutic purpose. Residual risk in general is the risk which cannot be excluded with absolute safety, but which can be regarded as enough improbable or insignificant to be considered legally acceptable in the face of the benefit offered by the risk source.

In a comparative setting, acceptable is the risk associated with a benefit source which is inferior to the risks associated with other sources bringing about the same benefit,<sup>8</sup> and is proportionate to the associated benefit.

After distinguishing between the different notions of risk within the pharmaceutical field (juridical, statistical-epidemiological, medical, personal risk), the chapter illustrates the risk management and communication system in the pharmaceutical setting. Interestingly, the legal notion of residual risk helps draw important distinctions about the role of communication in the field of health risk.

Risk communication to the concerned parties (doctors and consumers) and, when needed, to the public at large, can either serve as a warning to reduce risk and

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<sup>8</sup> Räßle, 1991: 110. Scheu, 2003: 713.

instruct about adequate use as to prevent avoidable risk, and/or as an instrument for allowing the autonomous decision about the residual risk.<sup>9</sup>

This double purpose is reflected in the liability regimes regulating both doctor's and pharmaceutical product information.

## **Chapter 2**

Chapter 2 deals with liability regulation concerning pharmaceutical product instruction and presents the two main liability regimes: tort and strict liability. Strict liability is related to unacceptable risks exceeding the legally established tolerability threshold, and gives rise to compensation independently of product instruction faults. Tort liability is related to product faultiness in design, manufacturing or related instructions. A drug which has no construction or manufacturing flaws can still give rise to compensation duties for damages caused by faulty instructions. PL information therefore acquires a fundamental importance in liability litigations concerning residual risk.

## **Chapter 3**

Chapter 3 deals with doctor's risk disclosure duties towards the patient. This is subjected to contract and tort liability and is divided into two broad categories: "Sicherungsaufklärung" (safety information) and "Selbstbestimmungsaufklärung" (information for self-determination)<sup>10</sup> in according to the distinction between avoidable and unavoidable risk associated to the therapy/intervention.

Safety information is aimed at preventing avoidable damage by instructing the patient as to a correct and safe therapeutic behavior (dosage, duration eventual precautions).<sup>11</sup> In the post-therapy phase, this can translate into information about the necessary measures for preventing complications and eventually insistence in the danger represented by non-compliance.<sup>12</sup>

Information for self-determination aims to make the patient knowledgeable of the residual risk connected to the therapy, and which must be taken into account because it is not ascribable to medical error.

Information for self-determination is a necessary condition for consent to be valid as established by the institute of informed consent which regulates doctor-patient interaction. In addition to information about the residual risk, this concerns also the expected benefit, probability of therapeutic success and in general any relevant data for an informed consent to the proposed therapy (economic costs, relevant alternatives).

The institute of informed consent is relatively recent and has begun to find its way in the U.S. legal system in the '50ies as a consequence of a new interpretation of

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<sup>9</sup> Hart, 1998b: 182.

<sup>10</sup> See also Francke, Hart, 1999: 55 ff.

<sup>11</sup> BGH 22.1.1960 (VersR 60, 417-19). See also Krudop-Scholz, 2005: 70.

<sup>12</sup> Francke, Hart, 1999: 49.

individual liberties and autonomy brought about by a new right-orientation (civil rights and consumer rights).<sup>13</sup> However, in Germany, the development of case law around the concept of “informierte Einwilligung” (German version of informed consent) dates back to 1894 with a court decision establishing that a doctor that commits a bodily injury *with no permission* of the patient acts tortuously because he violates the bodily integrity and health.<sup>14</sup>

Lacking a specific regulation on the matter, judges facing the task of determining compensation duties for the doctor have subsumed the medical intervention under 823.1 BGB which states that: “A person who intentionally or by his negligence, unlawfully causes death or injury or impairment of the health, freedom, property is bound to compensate him for damages arising therefrom”,<sup>15</sup> where compensation is linked to the qualification of the medical intervention as “Körper- und Gesundheitsverletzung” (bodily and health injury - tort liability).

In this context, consent serves the purpose of legitimizing the doctor’s intervention and safeguarding him from liability charges: “The tortuousness, and thereby the responsibility of the doctor according to 823.1 BGB is excluded only if – and to the extent that – the patient or his legal representative has consented to the lesion”.<sup>16</sup>

In order for consent to be valid however, it must be given in observance of the right to autonomy and self-determination<sup>17</sup>, and therefore must be preceded by adequate information about the intervention itself and consequent health implications.

As a consequence, the information delivered within the context of informed consent is a legal tool aimed at the distribution of the responsibility concerning the residual risk associated with a therapy or a medical intervention. Two critical aspects are questioned in the legal debate in this respect:

- on one side the institute of informed consent is considered an inadequate ground for the regulation of the doctor-patient relationship, because it equates the *doctor’s action* to that of a *knifer* (“Messerstecher”),
- but on the other side it is also criticized because it reduces the *doctor-patient communication* to a *risk disclaimer*.

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<sup>13</sup> Faden, Ruth. R, Beauchamp Tom L., *A History and Theory of Informed Consent*, (New York: Oxford University Press, 1986), pp. 23-143.

<sup>14</sup> Reichsgericht 31.5.1894, Strafs. Bd. 25, nr. 127: 375: “Ein Arzt der vorsätzlich für Heilzwecke eine Körperverletzung verübe, ohne sein Recht heilzu aus einem bestehenden Vertragsverhältnisse oder einer präsuntiven Zustimmung, dem vermuteten Auftrage hierfür legitimer Personen, herleiten zu können, handelt überhaupt unberechtigt, also rechtswidrig”.

<sup>15</sup> English translation from: Dietl, C.E., E. Lorenz, *Dictionary of Legal, Commercial and Political Terms* (2005). § 823 I BGB: “Wer vorsätzlich oder fahrlässig das Leben, den Körper, die Gesundheit, die Freiheit, das Eigentum, oder sonstiges Recht eines anderen widerrechtlich verletzt, ist dem anderen zum Ersatz des daraus entstehende Schadens verpflichtet”. The German formulation differentiates from other European equivalents in that it restricts the general clause to a specific list of goods protected by the constitution (s. Wagner, 2004:1473) and than extends the obligation to compensate to other goods only indirectly in the second paragraph through reference to specific laws (see later on).

<sup>16</sup> “Die Widerrechtlichkeit und damit die Haftbarkeit des Arztes aus 823 [I BGB] ist nur ausgeschlossen, wenn und insoweit der Kranke oder sein gesetzlicher Vertreter in die Verletzung eingewilligt hat”: Reichsgericht 14.3.1911, *Juristische Wochenschrift*, 1911: 450.

<sup>17</sup> Which follows from article § 1 I GG: „Die Würde des Menschen ist unantastbar. Sie zu achten und zu schützen ist Verpflichtung aller staatlichen Gewalt.“; and § 2 I GG: „Jeder hat das Recht auf die freie Entfaltung seiner Persönlichkeit, soweit er nicht die Rechte anderer verletzt und nicht gegen die verfassungsmäßige Ordnung oder das Sittengesetz verstößt“.

This debate has only recently found a solution with the disentanglement of indemnity for information failures from 823.1 BGB through the 2<sup>nd</sup> Amendment Law for Damage compensation.<sup>18</sup> In fact, through this law, compensation for moral damages (under which the violation of the right to self-determination falls) is also granted within contract liability. It has been observed that by allowing the claim for moral damages also for contract breaches, the legislator intends to steer the future medical liability law into its natural setting, namely breach of contract (rather than tort law)<sup>19</sup>.

Indeed, differently than in tort liability, within contract liability, the damage derived from the lack of self-determination information consists in the lost chance to decide upon one's own health, independently of eventual material damages. Therefore information for self-determination ceases to be a risk disclaimer and rather responds to the need of enabling the patient's autonomous choice within a counseling activity: risk information is only part of the more general duty of fostering a shared decision making.

This analysis constitutes the basis for examining the legal status of PL information within the institute of informed consent and for evaluating PL information within this institute.

## **Chapter 4**

Chapter 4 is devoted to analyze the legal nature of PL information within its interplay with doctor's information. From the analysis of statutory and case law it results, that in addition to the traditional safety function ascribed by safety regulation to product instruction (warning), PL information also plays an autonomous role within the institute of informed consent; precisely that of informing of all possible residual risks associated with the therapy, besides the risks which must be disclosed by the doctor according to the information duties established by judicature.

As a second step, fundamental objections are presented against the PL as an adequate source of information for the patient consent on legal grounds.

## **Part II Normative analysis of PL information**

The second part of the thesis is devoted to evaluate the adequacy of PL information to accomplish the legal functions established by the law and identified in the first part.

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<sup>18</sup> II Schadensersatzänderungsgesetz, 2SchadÄndG: 25.7.2002 BGBl I S 2674.

<sup>19</sup> „An die Einbeziehung des Schmerzensgeldanspruchs in die Rechtsfolgen vertraglicher Haftung hat der Gesetzgeber die Erwartung geknüpft, dass die *ihrer Rechtsnatur nach vertragliche Arzthaftung* künftig nicht mehr mithilfe des Deliktsrechts abgewickelt ist“. Ibid, citing the BT-Drucks. 14/7752: 15 (my emphasis).

Chapter 5 is devoted to the linguistic analyses of package leaflets, whereas chapter 6 presents a Bayesian analysis of PL information as a source of risk/benefit prognosis for the therapeutic decision.

## Chapter 5

Linguistic research<sup>20</sup> has analyzed PL texts as a token of expert-to-lay communication and has identified major sources of uncertainty induced by PL information in semantic and pragmatic factors such as ambiguity, vagueness, technical vocabulary and information overload.

However, the distinction between avoidable and unavoidable risk helps distinguish a further and more fundamental cause of uncertainty beyond textual content and design: the uncertainty typically affecting any decision under imperfect knowledge.

In fact the information about side effects (residual risk) results in prognostic uncertainty: this sort of uncertainty is inherent to the risk itself and does not simply result from background knowledge asymmetries due to expert-to-lay communication.

What is lacking therefore is the investigation of the contribution brought by PL information to the consumer's informed consent as a source of information within the specific decisional context inherent to lay therapeutic choice.

## Chapter 6

This chapter undertakes the task of answering the following questions:

1. What requirements the legislator establishes for consent to be qualified as informed;
2. Whether PL information fulfils these requirements.

As for the first point, the requirements are derived by the right which the institute of informed consent should honor, i.e. the right to self-determination: Information prior to consent should enable the patient to make an autonomous choice and therefore provide him with relevant data about the intervention/therapy and the risks and benefits involved. In order to allow a risk/benefit prognosis also probabilistic data about the healing effect and potential damage should be given.

The criterion of including probabilities as relevant information for choice mirrors the procedure developed in the framework of probabilistic decision making: Bayesian decision theory.<sup>21</sup>

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<sup>20</sup> Analyses range from text typology (Bock 1994; Donscheva 1990; Ehlich 1994; Ehlich/Noack/Scheiter 1994; Eckkrammer 1995, 1998, 1999, 2002, 2002b; Fickermann 1994; Grosse/Mentrup 1982; Hoffmann et al. 1998, 1999; Langer 1995; Mohn 1991; Nickl 2001; Werner/Heyne 1989) to lexicography (Mentrup 1982, 1988), and pragma-linguistics (Hensel 1989; Hoffmann, 1983; Saile 1984; Schuldt, 1992, 1998, Völzing, 1976, Zacharias, 1986).

<sup>21</sup> With the caveat that in the frame of informed consent – at least within the tort liability setting – the decision is understood as a yes/no option rather than a choice among several alternatives. The decision-maker needs to be made aware of the risks and benefits of the proposed intervention mainly. A duty to inform about alternatives is triggered only insofar they are attached with a significantly different

Bayesian theory results from the development of three distinct but interconnected fields of research devised in order to describe (and optimize) the management of decisions under uncertainty:

- 1) the theory of *decision optimization* through maximization of the expected utility;
- 2) the theory of *knowledge updating* through probabilistic induction;
- 3) the theory of *expected value of information* as a function of the expected reward in terms of contribution to decision optimization.

“Uncertainty” means in this framework an epistemic state of less than perfect knowledge about the actual state of affairs, which is modeled by a probability distribution/function over a state partition.<sup>22</sup>

The Bayesian approach to informed consent seems to underlie also the regulation of PL risk disclosure, as can be evinced from article 13.1 of the 1994 BfArM recommendations for PL information, which suggests to *give frequency of side effects whenever possible, in order to ease the risk estimation of the patient.*<sup>23</sup>

Thus, PL information is precisely thought of by the legislator as a source of probabilistic information for an autonomous decision, with related shouldering of residual risk.

In order to analyze the role of PL information in this setting, it has been considered its role as a contributor to epistemic accuracy within the therapeutic choice. The introduction of a Bayesian model for health choices accounting for the presence of genuine uncertainty (Andersson and Littkens, 2002) has allowed us to identify and distinguish relevant parameters in relation to the role of information in health decisions.

The model is constituted by a two-components function. The first component is a traditional expected utility function (where utilities are weighted by probability assignments); the second is a generalized expected utility where health statuses (utilities) are surrounded by uncertainty and cannot be assigned firm probabilities:

$$U(a) = \gamma(a) \cdot \sum_s \pi_s(a) u(h^s, a) + (1 - \gamma(a)) \cdot u_0(a).^{24}$$

Along this model, consent has been defined to be informed to the extent that it approaches a decision under risk (known probabilities), i.e. to the extent that the decision maker can assign a probability measure to each health status in a ranking from the most favorable to the worst – being health statuses nothing else than quantities of quality adjusted healthy days – and that he knows whether the act of

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risk/benefit profile. See chapter 3 § 4 for the distinction between contract vs. tort liability approach to informed consent.

<sup>22</sup> A decision under uncertainty differentiates from a decision under risk such as that of games of chance, where probabilities are objectively determined by the stochastic mechanisms underlying the game (1/6 probability for any die face in a throw, 1/52 of a Queen of hearts, etc.). However terminology slightly varies in the literature, especially objections are moved against the misleading use of the word “risk”: Gärdenfors, Sahlin, 1988: 5. Andersson and Littkens, 2002, which provide the model presented below speak of conventional risk for uncertainty with known probabilities, in the sense that the individual is sufficiently confident to assign a specific probability measure to the events under consideration, and of “genuine uncertainty” for a situation approaching ignorance, i.e. where the decision maker has a very vague of no idea about the probabilities which should be assigned to the relevant events.

<sup>23</sup> See original excerpt in chapter 4 § 4.2, footnote: 35.

<sup>24</sup> Andersson and Littkens (2002): 42.

taking the drug (a) shifts the probabilistic distribution towards stochastic dominance with respect to the act of not taking the drug.

This means that the weight factor associated to the first component of the utility function (which assigns a probability measure to each health status) tends to 1 ( $\gamma \rightarrow 1$ ). Against the framework of this model, PL information seems to provide the drug consumer with data whose personal relevance, and therefore prognostic value for the individual, is difficult to assess.

There are in fact no legitimate epistemic grounds for directly assuming this statistical frequency as a prognostic judgment about the probability that a single user might be concerned by the side effect.

In order for it to ground the prognostic assessment, PL information should be integrated with other parameters such as personal susceptibility given dosage/duration.

Given that side effects must however be taken into account by the drug user in accordance to the responsibility shouldered within informed consent, these data are bound to contribute to the weight factor assigned to the uncertainty component of the utility function.

Furthermore the probabilistic assessment should be combined with the perceived importance of the eventual damage (subjective disutility), the evaluation of which is most of the times hindered by the lay incompetence to appraise the magnitude and health implications of the risks mentioned in the PL.

This means that consent on the basis of PL information rather approaches a decision under ignorance than one under risk: as a prognostic device, PL information fundamentally asks more questions than it answers.

Given that the legislator implies that consent is given with knowledge of the probabilities of risks and benefits, PL information cannot be considered adequate for consent.

As for the safety function which PL information should also accomplish, so the contribution of PL information in this respect does meet minimal requirements, in that the drug consumer can actually profit from it in order to use the product correctly and safely. In this respect, also information about residual risk (side effects) accomplishes a safety function in that it might help the consumer identify eventual unexpected symptoms as side effects, whenever they are already listed in the text. Side-effect information can be validly used for diagnostic rather than for prognostic assessments.

The legislator should account for this asymmetry and regulate liability based on information consequently: the consumer should not be considered committable to residual risk on the basis of PL information, but instead it should be emphasized his contributory negligence whenever safety aspects of PL information are not sufficiently taken into account by him.

### **Part III**

#### **Empirical findings**

The third part presents a quantitative and a qualitative research on PL use. The final chapter integrates the results obtained in the empirical studies in a unitary model of health risk information processing.

Chapter 7 presents the results of an exploratory survey on the effect of PL information on the risk/benefit assessment of concrete drug users.

Chapter 8 investigates lay strategies for PL information selection and risk/benefit assessment through the material provided by a “think aloud experiment”.

Chapter 9 integrates Bayesian categories of analysis with bounded rationality theories in order to construct an integrated model of health risk information processing.

#### **Chapter 7**

Chapter 7 presents the data emerging from a survey based on a questionnaire administered to 55 drug consumers in the university campus. In order to investigate the impact of PL information, a sort of “paired comparisons test” has been devised. Questions related to the risk/benefit estimation and decision confidence were asked before and after reading the PL accompanying the drug.

The information impact was measured by the difference between risk/benefit assessment before and after reading the PL.

No significant change in the risk/benefit impact has been registered from the pre PL to the post PL phase. Contrary to commonly held opinions – but in line with recent studies – not all participants seem to get frightened by PL reading.

This apparently contradicts the perceived increased level of knowledge after reading the PL, which is the only statistically significant change among all assessments before and after the PL.

The data fundamentally hints at a gap between the perceived information value of package leaflets, and their concrete contribution to an autonomous choice. Furthermore the findings neither confirm nor disconfirm the supposedly uncertainty inducing effect generally attributed to PL information, instead they suggest that rather than being influenced by a vague prognostic uncertainty about all possible risks, the confidence in the therapeutic choice is mostly affected by the emergence of *specific* topics of concern.

The fact that no overall increased risk perception can be associated to PL reading, and that nonetheless the presence of specific topic of concerns is indeed associated with different risk and benefit perception patterns can be interpreted as a sign of no spill-over effect: *participants do not take seriously any item of risk information contained in the PL, but only specific items.*

The main result deriving from this study is however the gap between increased perceived level of information and

1. insignificant PL impact on benefit and risk assessments;
2. absolute no impact on the decision.

Considering the generally positive evaluation of PL information and the increased perceived level of information after PL reading, these data support the hypothesis that the therapeutic decision concerning prescription drugs is quite insensitive to PL information.

## Chapter 8

The qualitative study (chapter 8) enjoys the technique of the “think aloud” experiment. Participants have been asked to answer the questionnaire and read the PL in the presence of the analyst. Comments and answers to open questions give important insights as to the way drug consumers cope with the perceived unmanageability of PL information.

A contrasting feeling towards the package leaflet can be observed, which is explained through the phenomenon of “relevance paradox”: each item of PL information is perceived as potentially relevant for the drug consumer; but the probability that all of them jointly concern him is extremely low. This leads the single user to consider the text as *constitutively over-informative*.

PL information seems to raise more questions than it answers. Generally people perceive it as highly important, but are not in the position to adequately select personally relevant information. This might lead to the overload sensation accounted for through the notion of “relevance paradox”. Common heuristics to bypass these shortcomings are reappraisal, counterfactual neglect, idiosyncratic causal models, and uncertainty neglect.

As a result, PL information is not processed in its entirety and is selected through the most diverse filters.

A key for the selection of relevant information is constituted by the information provided by the doctor’s consultation: PL information which can be connected to what the doctor has already communicated is considered relevant; any incomprehensible data are considered to be addressed at the expert, and are therefore neglected. A space of uncertainty opens for risk information which has not been previously addressed by the doctor and is comprehensible: in this case uncertainty arises as to its possible occurrence.

The analysis allows to spot the institutional context in which the PL communication is embedded as the framework providing the pragmatic clues, through which PL information processing is at all possible. *Without the cues provided by the doctor’s information, the reader would find himself in front of an amount of unmanageable information, which only becomes intelligible through the knowledge previously acquired in the consultation.*

Therefore, any information with no relationship to any item of knowledge in one’s own database is perceived as irrelevant and dismissed as such. Paradoxically one might say here, that information that sounds “new” at this stage of post-consultation, will be considered irrelevant.

This raises some doubts as to the legitimacy of PL information as a basis for a the consumer’s informed consent.

Rather than being a basis for an evaluation of the treatment choice, the PL is conceived as a modular reference text to be consulted at the beginning for precautionary reasons, and then during the therapy in order to identify eventual side effects.

## **Chapter 9**

Chapter 9 posits the *therapeutic decision* as the teleological determinant for the information processing. Thereby, the therapeutic decision, which is established by the legislator as the communicative purpose of the PL text, suggests the theoretical framework within which the behavior concerning PL information processing can be investigated, namely: decision theory.

The theoretical structure is provided by the Bayesian theory of expected information value. This frame is integrated with the insights gained by cognitive approaches to information processing (“Bounded rationality” theory), and emotional accounts of health risk information processing.

The added value brought about by this integrated model is that it accounts for the accuracy level of PL information processing and impact by tracing them back to the decision sensitivity to the information at hand.

In particular, recurrent phenomena observed in the empirical literature – reappraisal, cognitive dissonance, information avoidance – are integrated in a comprehensive model including the structural factors which determine the expected value of information to decision, and the perceived capacity to deal with this information (self-efficacy).

The integrated Bayesian-cognitive model implies for instance that whenever no alternative is at sight, the cost of acquiring further information is considered worthless. Also when information is perceived as useful, but too demanding in terms of information design in relation to one’s own processing capacities it tends to be neglected.

## **Chapter 10**

The conclusive chapter summarizes the research results and proposes some suggestions for the legislator and for the text designer.

In particular it is proposed that the legislator clearly discriminates between the safety and the self-determination components of PL information as it is already distinguished in the regulation of doctor’s information.

A possible consequence of this distinction could be the partial disentanglement of PL risk disclosure from risk responsibility allocation.

Patient’s responsibility should be therefore articulated as follows:

- The patient’s contributory liability for damages caused by non-compliance to safety instructions should be maintained. Indeed along the analysis proposed in the thesis, this sort of information can be validly used by drug consumers for averting or minimizing risk.

- Instead PL information cannot be considered adequate for consent to be valid. Therefore it cannot offload the pharmaceutical firm from the responsibility related to residual drug risk, whenever the doctor cannot be considered liable for it. As a consequence strict liability of pharmaceutical firms should be extended to damages which are beyond the residual risk level, but which are nevertheless relevant for the damaged person.

These claims can be also supported by the consideration that damage liability is only a monetary compensation for injuries which touch high valued goods such as psychophysical wellbeing.

More generally, with an explicit separation of the safety and self-determination aspects related to PL information, patient's contributory negligence in safety issues could be more clearly emphasized and contribute to balance the distribution of responsibilities around drug consumption.

Although the research regards German pharmaceutical regulation, the thesis is written in English (American spelling) in order to make the results available to the widest possible audience.



# **PART I**

## **Pharmaceutical information and the law**



# 1 Product safety

## 1. The Janus-character of pharmaceutical products: sources of uncertainty and risk communication

The development of medicine and pharmacology after World War II has significantly contributed to a new attitude towards health and illness. Nowadays the multiplicity and sophistication of medical technologies has reached such a level that a specific term has been coined in order to describe this process: medicalization of the society.<sup>25</sup>

However, after a first phase of unlimited trust in the progress of medical sciences and pharmaceutical research in particular, a phase of disenchantment has followed as a consequence of shocking events which had deep direct and indirect impact on public awareness about pharmaceutical products.<sup>26</sup> These tragedies contributed to enhance efforts about possible ways to minimize the risk connected to drug use without renouncing to its benefits.<sup>27</sup>

Medicine and pharmacology show indeed a double identity: they both offer a kind of service to which anyone would gladly renounce for two reasons: the first and most obvious is that normally you would prefer not to need this service; the second is that the benefit of a therapy is always accompanied by a certain risk. Drugs have a Janus character as healing promise and poison at the same time.<sup>28</sup> Debates about

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<sup>25</sup> Zola, I. 1972; Camper, 1996; Domenighetti, 2005: 221 ff. ascribes the “surmedicalization de la vie” to three major factors: 1) the higher uncertainty in job market, with consequent stress and higher morbidity in the population; 2) the decrease of risk parameters levels such as cholesterol or hypertension so as to increase pharmaceutical market (so called disease mongering), and the overuse of diagnostics; 3) finally, population aging in western societies. The most worrying aspect of this state of affairs is represented by the limited economic resources in face of a potentially unlimited demand.

<sup>26</sup> See the case of a tranquilizer Contergan (Thalomid) in Germany: 2800 physically and/or mentally handicapped newborns from mothers using the drug during their pregnancy (1957-1961). More recently: Lipobay®, Vioxx®, and Bextra ®.

<sup>27</sup> For a detailed report about the last forty years of drug regulation in Germany and Europe see Sheu, 2003.

<sup>28</sup> Hart, 2005: 204.

pharmaceutical products focus on one and the same principle: Health as an individual and societal good, which drugs contribute both to promote and to endanger.

The need for preventing damaging events has led to a strict regulation of the pharmaceutical market. This has increasingly enriched the list of responsible care duties for dangerous entities<sup>29</sup>, and enlarged the intervention powers of the authority in charge.<sup>30</sup>

These measures though do not constitute an absolute guarantee of safety: however carefully designed and manufactured, pharmaceutical products can produce unpredictable reactions in the different organ systems. The awareness of this residual risk has led the legislator to regulate pharmaceutical safety through a risk prevention and management system.

Risk communication assumes in this context diverse functions in face of the uncertainties deriving from pharmaceutical products.

These uncertainties are of various natures and can be briefly described as follows:

1. *Epistemological* uncertainty about any specific product: because drug reactions are idiosyncratic and depend on several epidemiological and genetic factors, knowledge about the effects of any drug grows with the number of its users. This means that even many years after approval, it is still an “experimental product”<sup>31</sup>, the information about which is neither exhaustive nor conclusive.

To face this kind of uncertainty, the legislator has predisposed a *risk surveillance and management* system, with the aim to prevent and reduce risk to the minimum. *Risk communication among experts and to the public (top-down) proves to be a fundamental alarming tool.* Warning failures and risk miscommunication should be all the more stigmatized.

2. *Ontological uncertainty* affecting pharmaceuticals in general: differently than in the case of other products, where the damage is generally to be traced to product faults, in the case of drugs, health injuries can also be the result of the organic reaction to the drug components. Risk is inherent to pharmaceuticals even if no design or production defect affects them.

Against this type of uncertainty a *risk tolerance threshold* is established above which the drug is considered unsafe. It is a pragmatic answer to an unsolvable dilemma.

3. *Metrical-methodological* uncertainty: it concerns the risk/benefit assessment and evaluation themselves. Pharmaceutical risk and benefit are umbrella concepts, whose several dimensions are difficult to operationalize, and therefore to measure and compare.

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<sup>29</sup> Generally also accompanied by deontology codes of self-regulation from the side of the industry (Scheu, 2003: 59-60). See in the pharmaceutical field the BPI-Kodex (Bundesverband der Pharmazeutischen Industrie).

<sup>30</sup> For a historical contextualization of this evolution see Scheu, 2003. A fundamental reference to the evolution of risk regulation is Di Fabio, 1994.

<sup>31</sup> Drugs are products under constant testing („Arzneimittel sind Produkte in Dauererprobung“) declared the Health Minister Dr. Focke in the ministerial statement for the provision of the drug act '76. Scheu, 2003: 701.

Shortcomings of medical sciences in quantifying these dimensions might be compensated by a deeper understanding of the health implications related to the therapeutic choice according to the perspective of the most concerned parties (bottom-up communication).

4. The fourth type of uncertainty is *ethical* and is related to the risk tolerance threshold established through the risk/benefit assessment. This determines the level of socially accepted risk and it represents a compromise among the different stakeholders: also here communication among authority, pharmaceutical enterprises, the health professional and the public plays a decisive role. *Risk communication among stakeholders should build the basis upon which risk acceptability is established.*

At this level, communication is an indispensable tool for guaranteeing *decision autonomy through adequate risk information* and allow a personal risk/benefit evaluation (both for the doctor and for the end-user). It is within this framework that the nature of risk information to the patient through the package leaflets needs to be investigated.

In addition to these different sources of uncertainty, several concepts of risk intertwine and overlap in the pharmaceutical field.<sup>32</sup>

1. the legal articulation of the concept of risk in a rich dogmatic for
  - 1a. safety regulation
  - 1b. and the distribution of damage liability.
2. the statistical-mathematical notion of risk as analyzed through probabilistic models for the prognosis of drug effects;
3. the statistical-epidemiological survey of drug risks on a population;
4. the medical prognosis of risks for a specific risk group or individual;
5. the lay perception of risk and risk acceptance at societal level;
6. the lay perception of risk and risk acceptance at individual level.

These different conceptions are strictly interconnected. The legislator is continuously challenged to subsume under legal categories aspects of technology and scientific development which are difficult to control.

Risk communication plays two distinct roles in this setting. As for point 1a – safety regulation – risk communication among pharmaceutical/medical experts and administrators serves the purpose of helping experts coordinate their efforts for monitoring and reducing risk (in the sense 2-4), establishing acceptable risk thresholds (where legal norms are legitimized by scientific documentation) by eventually involving psychosociological dimensions (5 and 6). Moreover, transparent and timely communication is an essential tool for drug risk management. Within liability regulation (1b), risk communication among different stakeholders equates to a distribution of responsibility as for the consequences brought about by health technologies.

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<sup>32</sup> See also Preuss, S. 1996: 68.

The PL has emerged as a vehicle for risk communication to the end-user within safety regulation (risk avoidance/minimization), but has increasingly acquired liability relevance (distribution of risk responsibility). Moreover, it is embedded in a wide risk communication framework, where the risk information delivered by the doctor should constitute the principle channel for therapeutic communication. It is precisely in this framework that point 4 (medical tailored risk prognosis) and 6 (individual perception of risk) can come to collide because of the interference of PL information, and eventually lead to non-compliance.

The aim of this chapter is to illustrate drug safety regulation and the role of communication measures at each of the uncertainty levels mentioned above. The following chapters will investigate the function of risk communication as a distributor of risk liability.

## **2. Safety regulation in Germany**

Safety regulation has evolved through the specification of the professional duties of the pharmaceutical firm and of the intervention powers and duties of the responsible authority.

Specific professional duties concerning pharmaceutical enterprises were first articulated in the court decision following the Contergan trial.<sup>33</sup> It is thanks to this sentence that a general consumer protection and risk disclosure duty concerning the pharmaceutical firm have been established and concretized.

The first and foremost duty mentioned in the judgment is the obvious task of thoroughly investigating a chemical entity prior to marketing through pharmacological and clinical studies.

The general protection duty towards the consumer also determines the safety practices required after authorization. A sufficient protection for the consumer is not guaranteed when a pharmaceutical firm takes countermeasures against side-effects after they have been proven.<sup>34</sup> Because a positive proof of damage causality requires time, and a large epidemiological base – and can also never be definitively assessed – a scientific proof of causality cannot be a valid criterion for determining the threshold of safety countermeasures.

Neither is a scientifically founded suspicion an adequate condition for requiring safety measures. Before a risk suspicion can be founded scientifically, enough time may pass as to produce damage in some consumer. During this vacillation time, the risk has to be undertaken by the pharmaceutical firm. This translates into the implementation of adequate measures to reduce the risk (labeling changes, suspension of the product distribution, product retirement).

The risk linked to causal uncertainty falls primarily upon the producer and results in an obligation to adopt adequate actions, whenever the protection of the consumer requires it.

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<sup>33</sup> LG Aachen, 18. 12. 1970 – 4 KMs 1/68, 15 – 115/67. JZ 507 (521).

<sup>34</sup> LG Aachen, 18. 12. 1970, JZ 515.

Moreover, for the principle of inverse proportionality, and from the high importance of the goods at stake (health and possibly life) even very low probable suspicions ask for timely countermeasures.<sup>35</sup> General criteria for determining the opportunity and entity of safety actions are provided:

1. *severity* of the suspected health damages: the more dangerous the drug is supposed to be, the earlier and prompter must the firm react to risk news concerning the product;
2. the nature of the damages: *irreversible* damages require quicker reactions than transitory disturbances;
3. side effects *frequency*: the higher the frequency of risk data, the lower the suspicion needs to be in order to require safety countermeasures from the firm;
4. *therapeutic importance*: the higher the interests of patient in the availability of the drug, the higher can the risks be, that are taken into account in order to allow the drug to stay in the market. Therapeutic importance is determined by the lack of alternatives and the severity of the illness.

As for the question about which concrete measures shall be adopted, the answer changes from case to case, but depends fundamentally on the course of action, which allows the best possible protection of the consumer.

So, for instance, the further investigation of the causal connection between drug and damage does not have a direct impact on the protection of health, but rather serves to absolve the product from eventual imputations. More pertinent measures instead involve the adoption of *communication actions towards the health professional and the end-user*, the introduction of the prescription requirement, and possibly the retirement of the product from the market.<sup>36</sup>

The justification for the adoption of this safety regime can be summarized in the following points:<sup>37</sup>

1. pharmaceuticals are a special kind of product. No drug is void of side-effects, some of which can be identified only years after introduction into the market;
2. the causal assessment of side-effects as it is performed through clinical studies is not always feasible and sometimes also illegal and unethical, when the side effect under investigation is severe and irreversible, and the experiments require a re-exposition to the drug;

Consequently, the level of professional care required is characterized by high strong requirements. Any identifiable danger source must be defused as long as the possibility of damage is identified.

Furthermore, the threshold level for the adoption of safety measures is lowered to the level of well-founded suspicion, and depends on the gravity of the risk (the higher the supposed risk, the lower need to be the suspicion in order to require for countermeasures).

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<sup>35</sup> LG Aachen, 18. 12. 1970, JZ 516.

<sup>36</sup> LG Aachen, 18. 12. 1970, JZ 516.

<sup>37</sup> See Scheu, 2003: 759-60.

The Contergan decision has not only greatly contributed to the definition of the principles underlying professional duties related to the production and distribution of pharmaceuticals, but also – and more importantly judicially– to the shift of risk regulation from a mere danger avoidance towards a risk prevention system. This has resulted from the introduction of lower thresholds for the adoption of safety measures as those established by traditional causal requirements typical of classical safety regulation (police law): well-founded suspicion rather than causal connection between possible damage and danger source.

The introduction of this principle in the definition of professional duties for pharmaceutical firms has been mirrored by corresponding intervention powers granted to the responsible authority through the articulation of a specific law for pharmaceuticals.

## 2.1 State duties towards health as a constitutional good

Health is a good constitutionally protected in all western countries. It is also recognized that this good concerns not only the individual but also the society as a whole.<sup>38</sup> Indeed the protection of the individual health is intertwined with the safeguarding and promotion of public health.

The democratization of western societies honors this right through the principle of equal access to health services for everybody, and has led to the institution of national health institutions aimed at providing healthcare for all citizens on the basis of quality, efficacy, economical rationality, and satisfaction of patients as well as health professional.<sup>39</sup>

The German constitution grounds the state duty to protect the citizen from health impairment and lethal agents through Art 2 II GG<sup>40</sup> in connection with Art 1 I GG. Art 2 II GG establishes the right of the individual to inviolability of life, bodily integrity and freedom.<sup>41</sup> Art 1 I GG obliges the state to actively protect human dignity.<sup>42</sup> This implicates, that the protection of the goods mentioned in Art 2 II GG should translate not only in the prohibition to violate them, but also in the active protection from third party infringements.<sup>43</sup>

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<sup>38</sup> Francke, Hart, 1999: 80.

<sup>39</sup> See also Hamlin, 2002: 204.

<sup>40</sup> GG stands for “Grundgesetz”, the German Constitution.

<sup>41</sup> § 2 II GG: “(1) Jeder hat das Recht auf die freie Entfaltung seiner Persönlichkeit, soweit er nicht die Rechte anderer verletzt und nicht gegen die verfassungsmäßige Ordnung oder das Sittengesetz verstößt. (2) Jeder hat das Recht auf Leben und körperliche Unversehrtheit. Die Freiheit der Person ist unverletzlich. In diese Rechte darf nur auf Grund eines Gesetzes eingegriffen werden”.

<sup>42</sup> § 1 I GG: “(1) Die Würde des Menschen ist unantastbar. Sie zu achten und zu schützen ist Verpflichtung aller staatlichen Gewalt. (2) Das Deutsche Volk bekennt sich darum zu unverletzlichen und unveräußerlichen Menschenrechten als Grundlage jeder menschlichen Gemeinschaft, des Friedens und der Gerechtigkeit in der Welt. (3) Die nachfolgenden Grundrechte binden Gesetzgebung, vollziehende Gewalt und Rechtsprechung als unmittelbar geltendes Recht.”

<sup>43</sup> Scheu, 2003: 724.

In the case of pharmaceuticals however, the state's duty to protect the individual from third parties is also triggered by the citizens' domain-inexpertise and subsequent incapacity to protect himself from drug related risks.<sup>44</sup> In fact, the very protection of Art 2 II GG through drug selection prior to approval would constitute a violation of another constitutionally protected good, namely, the freedom of (therapeutic) choice (Art 2 I GG).<sup>45</sup> However, because of the enormous amount of information and data which this choice would presuppose you cannot *de facto* speak of a freedom of choice for the consumer.<sup>46</sup> Neither consumers' nor doctors would be able to make a rational decision among all possible pharmaceutical products, if these entered the market without any prior selection. Therefore they would not concretely exercise the right itself: it is precisely this impossibility on principle for the interested party that constitutes the basis for the authority subsidiarity.<sup>47</sup> Safety protection is a task that legislator, administrative authority, and case law (court decisions) jointly accomplish.

## 2.2 The German medicines act

Safety is legally defined as the absence (absolute safety) or at least the improbability (relative safety) of future offences to goods protected by the law.<sup>48</sup> The aim of police law is precisely to prevent the offence of such goods by averting damages. Therefore safety law is inherently preventive.<sup>49</sup> To the two legal concepts of "danger" (Gefahr) and "risk" (Risiko) correspond to different levels of intervention powers from the state.

*Danger* refers to the probable concrete possibility of the occurrence of a not irrelevant damage:<sup>50</sup> for instance a fire in a forest. Danger avoidance measures aim at preventing the danger emerging at all.<sup>51</sup>

The authority has the right to intervene in the measure that the damage probability is high and its gravity is severe. The rule for danger avoidance intervention is the classic formula of inverted proportionality: the greater the eventual damage, the lower the probability of occurrence needs to be for allowing authority intervention.<sup>52</sup>

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<sup>44</sup> Pitschas, 1998: 228

<sup>45</sup> See also Hart, 2005: 211

<sup>46</sup> This is the reason why the general point of view, according to which the selection of products should be let to the market alone solely on the bases of their market behavior, is not legitimate in this specific field. Wolz, 1988: 9-25.

<sup>47</sup> Wolz, 1988: 21.

<sup>48</sup> Dettling, 2005: 162-63.

<sup>49</sup> Dettling, 2005: 163.

<sup>50</sup> Dettling, 2005: 163. Di Fabio, 1993: 110: "Eine Gefahr ist nach den allgemeinen Regeln des Rechts der Gefahrenabwehr nur dann zu bejahen, wenn ein Schadenseintritt an geschützten Rechtsgütern wahrscheinlich ist".

<sup>51</sup> Scheu, 2003: 71.

<sup>52</sup> The concept of probability as a legitimating factor for state intervention was originally defined by mere possibility of occurring. With the complex evolution of modern society into a risk society, it has become a relational factor dependent on the damage dimensions. Di Fabio, 1993: 110. "Der Begriff der Wahrscheinlichkeit entwickelte sich bereits in der allgemeinen Dogmatik des Gefahrbegriffs von einer

*Risk* refers to the awareness of an abstract possibility of a hypothetical damage with no concrete menace of occurrence: for instance adverse drug reactions.<sup>53</sup>

Risk prevention measures presuppose the establishment of a *tolerable risk threshold level over which intervention is demanded*.<sup>54</sup> It is the establishment of this risk threshold that decides when and if countermeasures are to be taken.<sup>55</sup> The formula of inverted proportionality does not refer to the concrete possibility of occurrence but to the abstract statistical incidence.

Neither does any casual connection need to be established between the eventual damage and the risk source: the only plausibility of the link between the two suffices for authorizing risk reduction measures. Given the high value of constitutional goods such as life and health, even low probabilities of connection are sufficient for intervention.<sup>56</sup> With the principle of risk prevention (*Risikovorsorgeprinzip*) the possibility of damage is taken into account, for which a causal link with the hypothesized source can neither be established nor denied.<sup>57</sup>

Eventual damage should not only be concretely averted, but also anticipated through continuous monitoring of sources of danger.

Increasing risk awareness in the society and the consequent lowering of thresholds for legitimate intervention has led to the evolution of safety regulation from mere danger avoidance to risk prevention.<sup>58</sup>

Both intervention conditions for danger avoidance and risk prevention makes reference to the probability concept. In the first case though, this is simply applied to the damage and its objective *possibility of occurrence*; while in the second, it is an epistemological judgment about the *hypothesis that the danger source is the real cause* for the possible damage under consideration.

With the German Medicines Act 1976 (henceforth AMG: Arzneimittelgesetz), also pharmaceutical safety regulation has evolved from mere danger avoidance (*Gefahrenabwehr*) to a risk prevention system (*Risikovorsorge*).<sup>59</sup> This has resulted both from the evolution of the probability concept for *legitimizing intervention* – the principle of well-founded suspicion<sup>60</sup> instead of the causality requirement – and also

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überwiegenden Möglichkeit zu einer wertungsabhängigen Risikoeinschätzung. Je größer der befürchtete Schaden desto geringer die Anforderungen an den verlangten Wahrscheinlichkeitsgrad”.

<sup>53</sup> Dettling, 2005: 163.

<sup>54</sup> Dettling, 2005: 164.

<sup>55</sup> Dettling, 2005: 164.

<sup>56</sup> Scheu, 2003: 70-73. Räßle, 1991: 97. The probability judgment in case of danger regards the eventuality of damage occurrence. In the case of risk, it relates rather to the causal link itself: Räßle, 1991: 79.

<sup>57</sup> BverwGE 72, 300/315, cited in Scheu, 2003: 73.

<sup>58</sup> “Eine sich selbst produzierter Risiken zunehmend bewusster Gesellschaft bewertet alte oder neue Schadenspotentiale immer höher und senkt demgemäß die Eingriffsschwelle, die durch das Wahrscheinlichkeitsmerkmal markiert wird”: Di Fabio, 1993: 111.

<sup>59</sup> This evolution has not cancelled the previous powers of risk intervention but rather extended them. So that it is possible to speak of danger avoidance *and* risk prevention system.

<sup>60</sup> Wolz, 1988: 1, 5.

from the integration of scientific criteria in the determination of the intervention *threshold*.<sup>61</sup>

The first law regarding pharmaceuticals dated back to 1961 and did not impose any authorization procedure, but just required a formal registration for any pharmaceutical introduced into the market. It was still a norm of danger avoidance:

- according to the legislator, it should be a duty of the state to regulate the production of pharmaceuticals so as to completely prevent health damages to the population;<sup>62</sup>

- the intervention criterion in case of danger required a causality assessment.

This causality requirement of AMG '61 (Arzneimittelgesetz: AMG) had the effect of thwarting the prohibition norm, given the methodological difficulties associated with causal assessment in medicine.<sup>63</sup>

On the wave of public bewilderment after the tragic pharmaceutical scandals, the legislator recognized that drugs are no ordinary products, and that the production of pharmaceuticals is a public task.<sup>64</sup> This led to a complete new version of the law as a risk prevention and consumer protection norm, issued in 1976.<sup>65</sup>

The AMG is part of a system of regulation, which guarantees the safety of pharmaceutical products. The other laws covering this health sector comprise the norms related to drug circulation (especially pharmacy law), civil and criminal liability (of the pharmaceutical company and of the state), norms related to information and advertising of pharmaceuticals, the regulation of doctors' professional duties and liability, and public insurance legislation.<sup>66</sup>

It was emanated in its actual form in 1976 and is the result of the political debate followed to the thalidomide tragedy (Contergan) and of the implementation of the European directives 75/318/EEC and 75/319/EEC, themselves following from this pharmaceutical catastrophe.<sup>67</sup>

The law incorporates the professional duties imposed on a pharmaceutical firm, as they had been delineated by the Contergan court decision.<sup>68</sup>

The explicit purpose of the law for pharmaceuticals is the safety of drugs administered to the public through the establishment of criteria for the efficacy, quality and safety ("Unbedenklichkeit") evaluation of candidate drugs.<sup>69</sup> It warrants for safety through drug approval, surveillance and liability norms.

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<sup>61</sup> See Di Fabio, 1993: 112.

<sup>62</sup> Scheu, 2003: 685.

<sup>63</sup> Wolz, 1988: 109. See § 4.2 on causal assessment of drug adverse events.

<sup>64</sup> Wolz, 1988: 2.

<sup>65</sup> Scheu, 2003: 720. Emergence and evolution of the law have gone hand in hand with European regulation on the subject.

<sup>66</sup> Francke, Hart, 1999: 81.

<sup>67</sup> Scheu, 2003: 755.

<sup>68</sup> LG Aachen, 18. 12. 1970, JZ 507 (521). See above: 24-25

<sup>69</sup> § 1 AMG: „Es ist der Zweck dieses Gesetzes, im Interesse einer ordnungsgemäßen Arzneimittelversorgung von Mensch und Tier für die Sicherheit im Verkehr mit Arzneimitteln, insbesondere für die Qualität, Wirksamkeit und Unbedenklichkeit der Arzneimittel nach Maßgabe der folgenden Vorschriften zu sorgen“. The term „Unbedenklichkeit“ refers to a safety judgment based on a risk/benefit assessment and equates to the term safety used in European regulation (Scheu, 2003).

Risk prevention is promoted by AMG through a strict regulation of *competences*, the establishment of quality and *safety requirements*, the institution of a *surveillance system*, and finally through norms regulating *risk disclosure* when this cannot be avoided.

Competent federal authorities are the Federal Institute for Medicines and Medical Devices for drugs in general (BfArM: Bundesinstitut für Arzneimittel und Medizinprodukte) and the PEI (Paul Ehrlich Institut) for blood products, sera, allergens, vaccines, and pharmaceutical products derived from tissues, bone marrow, genetic and cell pharmaceuticals. The federal office for consumer protection and food safety (BVL: Bundesamt für Verbraucherschutz und Lebensmittelsicherheit) is responsible for drugs for veterinary use (§ 77).

All decisions concerning pharmaceutical approval – approval grant, withdrawal, revocation or suspension – belong to the administrative authority (§ 25). Primary task of the administrative authority is therefore to take care of the safety of pharmaceuticals present in the market. This translates in an administrative activity which is grounded in scientific data provided by the different stakeholders (pharmaceutical companies, doctors, independent research) and in cooperation with other safety agencies at European and international level (EMA, WHO).<sup>70</sup>

Approval through the administrative authority however does not diminish the company's civil and criminal liability for torts or crimes.<sup>71</sup>

The competent authority is also liable for taking adequate measures as to remove breaches against pharmaceutical regulation or prevent future violations (§ 69 I) – coherently with other warning and safety measures<sup>72</sup> – to the extent that their activity is required by the obligation to protect health from danger coming from the drug. In particular they have the authority to prohibit the circulation of a pharmaceutical, or to order recall and confiscate it when approval or registration is not available or has been suspended (§ 69 I 1); the active ingredient does not comply to quality standards (§ 69 I 2); when benefit is wanting (§ 69 I 3); or there is a well founded suspicion that the risk exceeds the tolerable threshold as established by medical science (§ 69 I 4).

Risk prevention is managed through two control systems: drug approval (Verbot mit Erlaubnisvorbehalt: “default” prohibition with reserve of permission) and the post-marketing control.

Liability norms also constitute an indirect incentive to safety beyond their principal compensatory aim.

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<sup>70</sup> Francke, Hart, 1999: 89.

<sup>71</sup> § 25 X: “Die Zulassung lässt die zivil- und strafrechtliche Verantwortlichkeit des pharmazeutischen Unternehmers unberührt.”

<sup>72</sup> Binding of approval to the enforcement of particular warnings (§ 28 I, II); or to the prescription of further pharmacological and toxicological research (§ 28 III); causes for approval withdrawal, recall, suspension (§ 30); approval prolongation refusal because of causes for withdrawal, recall or suspension (§ 31 IV).

In general, AMG interferes in the pharmaceutical market through legal instruments of different categories:<sup>73</sup>

- The norms for the authorization of administrative acts and ordinances constitute the general regulative aspect of the law. These norms are part of the state's obligation to danger avoidance and risk prevention;
- The repressive norms of criminal law and against breaches of administrative rules (§§ 95 ff.) represent the second regulation level, through which transgressions of ordinances or prohibitions are subject to penal sanctions;
- Finally, civil liability norms (§§ 84 ff.) ground the legal basis for damage compensation duties from the pharmaceutical firm towards the user.

The law is divided in several sections and subsections. I present a succinct inventory with special attention to norms related to risk communication.

*Section 1. Purpose of the law and terminological definitions* (§§ 1-4 AMG).

*Section 2. Requirements for drug approval and circulation.* It comprises criteria for the establishment of the tolerated risk threshold and the prohibition of circulation for drugs, whose risk exceeds this threshold (§ 5); competent authority (§ 6); fraud prohibition (§ 8); responsible agent for drug circulation: pharmaceutical entrepreneur (§ 9); product labeling (§§ 10: package labeling; 11: patient package leaflet; 11a: information leaflet for the doctor; 12: authority powers concerning warning enforcement).

*Section 3. Drug production requirements* (§§ 13-20).

*Section 4. Drug approval:* approval duty (§ 21); application documents (§§ 22-24); clauses of approval refusal and approval decision process (§ 25-27); special conditions for approval linked to information duties (§ 28, 29); approval withdrawal, revocation, suspension (§ 30) approval extinction and prolongation (§ 31); other competencies of the administrative authority regarding approval (§§ 32-37), among which information of administrative acts to the public (§ 34).

*Section 5. Drug registration* (§§ 38-39): it concerns homeopathic drugs and herbal products for which no approval process is required.

*Section 6. Good clinical practice* (§§ 40-42): protection of test persons within clinical studies prior to approval.

*Section 7. Pharmaceutical distribution* (§§ 43-53): authorized agents for the distribution and administration of pharmaceutical products, prescription duty, and exceptions to the requirement of pharmacy sale.

*Section 8. Production quality controls* (§§ 54-55).

*Section 9. Special norms for veterinary drugs* (§§ 59-61).

*Section 10. Drug risk monitoring, survey and evaluation* (§§ 62-63): risk management coordination duty of the competent authority, cooperation with other competent institutions at European (EMA) and international level (WHO), and *authority to inform the public about measures which are intended to be undertaken*

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<sup>73</sup> Wolz, 1988: 4. Francke, Hart, 1999: 88: In addition to safety regulation, also the existence of public insurance and its mediating function in the provision of pharmaceuticals to the patient, contributes to the configuration of the pharmaceutical market as a publicly financed market, and therefore not private and free.

(§ 62);<sup>74</sup> § 63 “Stufenplan” – risk management plan comprising disclosure duties of the pharmaceutical firm (§ 63b).

*Section 11. Authority inspection and general notification duties towards and among authorities; intervention powers of the competent authority (§§ 64-69):* inspection process (§ 64); sample drawing (§ 65); cooperation duties by inspection activities (§ 66); general duty to give notice about pharmaceutical product development, manufacturing, clinical testing, storage, packaging, marketing, or commercialization in general (§ 67); centralized system of information gathering in the DIMDI data bank (Deutsches Institut für Medizinische Dokumentation und Information – German Institute for Medical Documentation and Information) (§ 67a); communication duties among competent authorities at state, federal, and European Commission level (§ 68).

*Section 12. Special norms for Federal Armed Forces, Federal Police, riot police, civil protection (§§ 70-71).*

*Section 13. Import and export regulation (§§ 72-73).*

*Section 14. Responsible appointee for pharmaceutical information and medical representative (§§ 74-76):* the high importance of continuously updated and correct information for drug safety is underlined by the norm concerning the appointment within the pharmaceutical enterprise of a person in charge of information quality and correctness.<sup>75</sup> This delegate is personally responsible for the information accompanying the product and must have an adequate medical/pharmaceutical university degree and a minimum experience of two years in the field.

Furthermore medical representatives are appointed as mediators between the pharmaceutical company and the health professional. The task of medical representatives is to provide the health professional with detailed scientific information about the product and to inform the employer in written form of any communication received by the health professional (§ 76).

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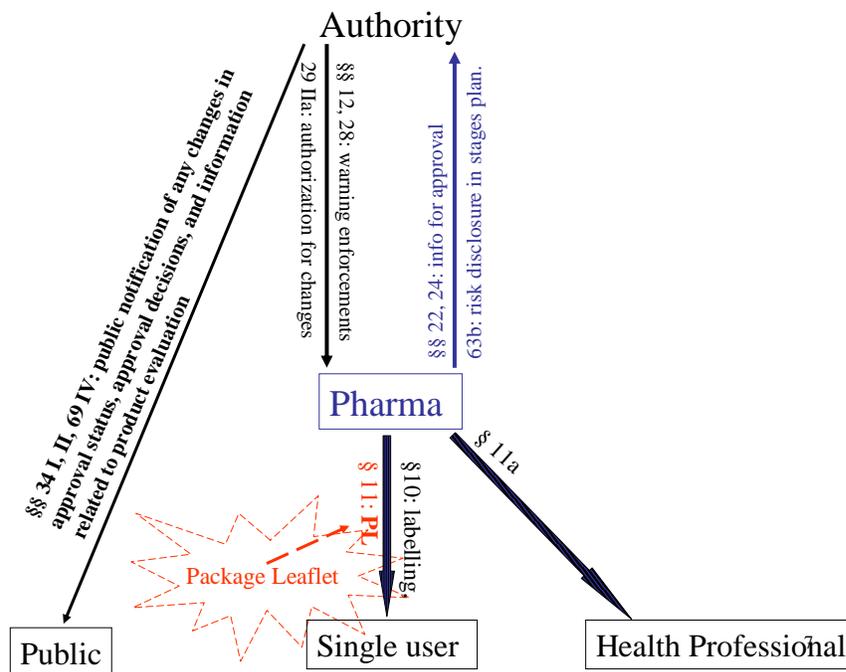
<sup>74</sup> § 62 AMG: „Die zuständige Bundesoberbehörde hat zur Verhütung einer unmittelbaren oder mittelbaren Gefährdung der Gesundheit von Mensch oder Tier die bei der Anwendung von Arzneimitteln auftretenden Risiken, insbesondere Nebenwirkungen, Wechselwirkungen mit anderen Mitteln, Verfälschungen sowie potenzielle Risiken für die Umwelt auf Grund der Anwendung eines Tierarzneimittels, zentral zu erfassen, auszuwerten und die nach diesem Gesetz zu ergreifenden Maßnahmen zu koordinieren. Sie wirkt dabei mit den Dienststellen der Weltgesundheitsorganisation, der Europäischen Arzneimittel-Agentur, den Arzneimittelbehörden anderer Länder, den Gesundheits- und Veterinärbehörden der Bundesländer, den Arzneimittelkommissionen der Kammern der Heilberufe, nationalen Pharmakovigilanzzentren sowie mit anderen Stellen zusammen, die bei der Durchführung ihrer Aufgaben Arzneimittelrisiken erfassen. *Die zuständige Bundesoberbehörde kann die Öffentlichkeit über Arzneimittelrisiken und beabsichtigte Maßnahmen informieren*“ (My emphasis).

<sup>75</sup> § 74a AMG: “Informationsbeauftragter. (1) Wer als pharmazeutischer Unternehmer Fertigarzneimittel, die Arzneimittel im Sinne des § 2 Abs. 1 oder Abs. 2 Nr. 1 sind, in den Verkehr bringt, hat eine Person mit der erforderlichen Sachkenntnis und der zur Ausübung ihrer Tätigkeit erforderlichen Zuverlässigkeit zu beauftragen, die Aufgabe der wissenschaftlichen Information über die Arzneimittel verantwortlich wahrzunehmen (Informationsbeauftragter). Der Informationsbeauftragte ist insbesondere dafür verantwortlich, dass das Verbot des § 8 Abs. 1 Nr. 2 beachtet wird und die Kennzeichnung, die Packungsbeilage, die Fachinformation und die Werbung mit dem Inhalt der Zulassung oder der Registrierung oder, sofern das Arzneimittel von der Zulassung oder Registrierung freigestellt ist, mit den Inhalten der Verordnungen über die Freistellung von der Zulassung oder von der Registrierung nach § 36 oder § 39 Abs. 3 übereinstimmen.”

15. *Competent federal authorities (§ 77); conflict of interests (§ 77); federal authority competence for veterinary drugs prices (§ 78) special authorizations in emergency cases (§ 79); authorization for procedure regulation in emergency cases (§ 80); AMG relationship to norms concerning atomic energy, animal protection, and psychotropic drugs (§ 81); general administrative prescriptions (§ 82); implementation of European Community Directives (§ 83).*
16. *Civil liability for pharmaceutical damage (§§ 84-94).*
17. *Criminal liability for non compliance to pharmaceutical regulation (§§ 95-98).*
18. *Law amendments and transition prescriptions.*

AMG norms regulate information duties and authorizations among the different stakeholders. Information regulation concerns risk disclosure duties from pharmaceutical company towards the authority and the public: the patient package leaflet is the main vehicle of direct communication to the user and its configuration is strictly regulated by AMG. Furthermore AMG establishes authorization powers assigned to the competent authority: these comprise not only approval of product information but also enforcement of special warnings when deemed necessary for health protection. After approval, risk management procedures determine “information vehicles and channels”.<sup>76</sup>

The following chart represents the information pyramid as it is shaped by AMG regulation:



**Figure 1: Pharmaceutical information regulation through German Medicines Act (Arzneimittelgesetz: AMG).**

<sup>76</sup> AMG § 63: “In dem Stufenplan können ferner Informationsmittel und –wege bestimmt werden”.

AMG regulates communication channels between: authority and the public, authority and the pharmaceutical firm; pharmaceutical firm and single user/health professional.

- *Authority towards the public:*

§ 34 I: The competent authority must notify any change in the approval status in the Federal Gazette. Furthermore they must make information regarding the granting of approval, the evaluation of pharmacological experiments results and clinical tests publicly available (§ 34 Ia). Also free access to approval decisions must be guaranteed (§ 34 Ib). In general any administrative act which concerns more than 50 people may be publicly notified by the authority (§ 34 II).

In case of approval recall, the competent authority can also publicly notify the administrative act (§ 69 IV).

- *Authority towards pharmaceutical firm:*

§ 12 I: the federal authority has prescriptive powers over labelling, package and specialist information, and can order that the quantity of specialist information be expanded with further data; they are furthermore entitled to prescribe that product information be transmitted through additional means other than package labelling and leaflet; and to enforce special warnings for specific drug groups.

§ 28: the federal authority is entitled to bind approval to special conditions, among others the imposition of specific information duties as for the correct product preservation and risk prevention.

Any modification in the information accompanying the product must be granted by the authority prior to execution (§ 29 II a)

- *Pharmaceutical firm towards authority:*

§ 22: the documentation for approval application is strictly standardized and comprises reports of chemical, (micro-) biological experiments, clinical trials, and pharmacological tests; package leaflet and summary of product characteristics as well as expert opinion as to the evaluation of quality control methods and test results (§ 24). Approval is to be granted on the basis of the documentation and expert opinion provided for approval application (§ 25 V)<sup>77</sup> and following a hearing from the approval commission (§ 25 VI).<sup>78</sup>

§ 29: the pharmaceutical sponsor is obliged to disclose any change in the information and documentation for approval. A disclosure duty also concerns any new data which might influence the drug risk/benefit assessment.

Within the drug risk management process (stages plan – “Stufenplan”), the pharmaceutical company is obliged to promptly refer any severe or not expected adverse event, and to provide the authority with periodical reports (§ 63b).

- *Pharmaceutical firm towards user:*

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<sup>77</sup> § 25 V AMG: “Die Zulassung ist auf Grund der Prüfung der eingereichten Unterlagen und auf der Grundlage der Sachverständigengutachten zu erteilen”.

<sup>78</sup> § 25 VI AMG: “Vor der Entscheidung über die Zulassung eines Arzneimittels, das der Verschreibungspflicht nach § 48 Abs. 2 Nr. 1 unterliegt, ist eine Zulassungskommission zu hören. Die Anhörung erstreckt sich auf den Inhalt der eingereichten Unterlagen, der Sachverständigengutachten, der angeforderten Gutachten, die Stellungnahmen der beigezogenen Sachverständigen, das Prüfungsergebnis und die Gründe, die für die Entscheidung über die Zulassung wesentlich sind, oder die Beurteilung durch die Gegenschverständigen. Weicht die Bundesoberbehörde bei der Entscheidung über den Antrag von dem Ergebnis der Anhörung ab, so hat sie die Gründe für die abweichende Entscheidung darzulegen”.

§ 8: protection norm against fraud (false labelling, indication of therapeutic effects which do not correspond to reality, declaration of certain benefit or of no side-effects);

§ 10: package labelling,

§ 11: package leaflet (PL).

- *Pharmaceutical firm towards health professional*

§ 11a: summary of product characteristics (SPC).

The regulation of information from health professional towards pharmaceutical firm or authority and vice-versa is outside the competence field of AMG. However the spontaneous surveillance system heavily relies on physicians' contribution to drug monitoring, and explicitly obliges the pharmaceutical company to notify any suspicious risk reported by health professional (§ 63b II 2a). Moreover doctors are must report adverse event cases by the Medical Association Code (§ 6 MBOÄ 1997).<sup>79</sup>

AMG deals with risk communication as an instrument of agreement about risk acceptability, as a tool for risk prevention and management, and finally, as a support for the safeguard of decisional autonomy.

Thorough investigation has already been devoted to the nature of administrative (communication) actions within the framework of police law and safety regulation.<sup>80</sup>

Little attention has been devoted instead to the qualification of product information for the patient in the form of package leaflets (PLs).

The official qualification of this form of information as product instruction for safe use does not exhaust its function. Beyond safety concerns, the presence of detailed information about residual risk, which is per definition unavoidable, cannot but be interpreted as a form of communication for an informed therapeutic decision, in analogy to information duties regulating doctor-patient relationship.

In this respect information about avoidable risk (instruction about adequate use, dosage and duration, contraindications, drug interferences, overdosage) and residual risk (side-effects associated with the drug) require and allow different responses from the reader: the former type of risk information demands the reader to comply to the instructions provided so as to avoid any undesired effects (safety aspect), in the latter case instead, no countermeasure can be taken in order to prevent side-effects to occur – apart from interrupting the therapy and informing the doctor, when reactions have already occurred. The only purpose of warning the reader about them, can only be to allow the user decide whether to undergo the risk listed in the PL or not, by putting him into notice (autonomy aspect).

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<sup>79</sup> Information in the pharmaceutical field is also regulated by the Drug Advertising Act (Heilmittelwerbengesetz: HWG) and indirectly by liability norms related to product instruction. I will not indulge on the former law, as it is marginal to the investigation of package leaflet. Instead I will deal with liability regulation extensively in chapters 2 to 4.

<sup>80</sup> See a. o. Egert, Osimani forthcoming; Hart et al. 1998; Hart 1998a; Pitschas 1998; Domeyer 1998; Sickmüller 1998; Deutsch, 1997; Di Fabio, 1993, 1994; Damm, Hart, 1993; Brandt, 1993; Paschke, 1993.

The present dissertation aims to analyze the role of PLs within the legal framework in which they are embedded, and than to investigate the extent to which its epistemic contribution is adequate for accomplishing the task it is supposed to fulfill.

## 2.3 Pharmaceutical product safety

Safety norms for pharmaceuticals regulate residual risk and development risk by establishing:

- principles and procedures for assessing the residual risk thresholds according to which a product can be allowed/forbidden to circulate in the market;<sup>81</sup>
- principles and procedures for intervention and risk prevention measures (well founded suspicion of unacceptable risk and risk management).

A central norm of AMG in this respect is § 5.<sup>82</sup> This is a prohibition norm that stipulates circulation prohibition for unsafe drugs and provides the related definition: according to § 5 II, unsafe drugs are such that on the basis of available scientific data, there is the well-founded suspicion that, by adequate use, they produce damage, which is beyond the threshold tolerated by medical sciences.<sup>83</sup>

This definition is articulated in four main components:

1. The degree of association between risk and danger source needed for intervention (“well-founded suspicion”);
2. the tolerance threshold (residual risk);
3. unsteadiness of approval status as a result of continuous drug profile updating (development risk);
4. and the reference to medical sciences as the perspective through which the tolerance threshold shall be drawn.

### 2.3.1 Intervention principle: well founded suspicion

The general recognition of the limited and fragmentary causal knowledge affecting especially chemical and pharmaceutical technologies has contributed to the awareness that criteria for the management of *not-knowledge* are needed.<sup>84</sup> The

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<sup>81</sup> The requirement of approval is prescribed by § 21 I AMG. The decision of approval is regulated according to § 25 with reference to § 5. The authority can reject an application for approval, only in case one of the conditions mentioned in paragraphs § 25 Abs. 2 or 3 AMG are not met. These conditions refer to therapeutic efficacy, (§ 25 II S. 1 Nr. 4 AMG), and adverse reactions (§ 25 II S. 1 Nr. 5 AMG) in that the risk tolerance for each treatment is decided upon its indication and therapeutic effect.

<sup>82</sup> Authority for intervention is linked to this norm throughout the law: § 25 II S 1. Nr. 5 (approval) in connection with § 28 (special conditions), § 30 (approval withdrawal, revocation, suspension), and § 69 I S. 2 Nr. 4 (risk management interventions). Hart, 1998b: 168.

<sup>83</sup> § 5 II: “Bedenklich sind Arzneimittel, bei denen nach dem jeweiligen Stand der wissenschaftlichen Erkenntnisse der begründete Verdacht besteht, dass sie bei bestimmungsgemäßem Gebrauch schädliche Wirkungen haben, die über ein nach den Erkenntnissen der medizinischen Wissenschaft vertretbares Maß hinausgehen”.

<sup>84</sup> Enquete-Kommissions-Bericht “Schutz des Menschen und der Umwelt”: BT-DrS. 12/8260, cited in Scheu, 2003: 72. In addition to inherent epistemological limits, Scheu also mentions the objective information insufficiency regarding the risk profile of chemical products in general. For most of the

“well-founded suspicion on the basis of available scientific data” substitutes the adequacy condition required in AMG '61 as for the degree of association needed for intervention. The term suspicion is defined as *hypothesis* of causal connection.<sup>85</sup> As already mentioned, this terminological modification is the reflection of a new understanding of the risk represented by drugs as unavoidably unsafe products<sup>86</sup>, for which the requirement of causal assessment is too demanding and therefore not adequate for timely measures to risk emergencies.

Given that the causal nexus can be seldom proven, waiting for the establishment of a causal connection before intervening would most times lead to late intervention and irreparable damage. Therefore “softer” epistemological concepts such as frequency of association serve the purpose of providing a reference tool for risk decisions.

The legal notion of suspicion is less demanding than that of cause, and in the case of pharmaceuticals, it begins as soon as a doctor assesses an association between a side effect and a drug.<sup>87</sup> However, the modifier “well founded” puts limits to the looseness of this requirement: the suspicion must be founded on concrete facts and cannot be justified by simple hypothetical speculations.<sup>88</sup> The facts supporting the suspicion do not necessarily need to be concrete cases of damage: also the acquisition of new substantial theoretical knowledge can ground risk suspicion, especially when there is little or no experience with the drug, which could refute the theory.<sup>89</sup>

The concept of suspicion has precisely been devised in order to regulate cases of decisions under uncertainty, where a resolution is administratively required and cannot be put off even in the absence of perfect knowledge.<sup>90</sup> In case of doubts about product toxicity the legislator is allowed and supposed to protect the user by undertaking adequate measures (from alerting measures to product retirement from the market).<sup>91</sup>

The risk prevention principle (Risikovorsorgeprinzip) applies whenever, as a consequence of scientific uncertainty, there is no positive knowledge about the threatening hazard.<sup>92</sup>

Epistemological limits spread out of the complexity of the systems involved (human organ and/or environment) and of the fragmentary and progressive nature of science. This structural uncertainty demands a flexible intervention rule: differently than in for danger avoidance, risk prevention applies the principle of proportionality not to

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chemical products on the market, fundamental data about chemical behavior and environmental consequences of their use are simply not available (Scheu, 203: 80).

<sup>85</sup> Scheu, 2003: 113.

<sup>86</sup> Scheu, 2003: 692.

<sup>87</sup> Di Fabio 1993: 125. The establishment of well founded suspicion in the single case is however more complex and an eventual solution seems to be far from being reached without the united efforts of medical and legal experts. See § 4.2 on causal assessment.

<sup>88</sup> Di Fabio, 1993: 125.

<sup>89</sup> See Di Fabio, 1993: 126-127.

<sup>90</sup> Di Fabio, 1993: 113.

<sup>91</sup> „Der Schwebezustand einer unsicheren Bewertung soll nicht vom Patienten getragen werden, der unter Umständen irreversible Gesundheitsschäden erleiden kann“: Hielscher, Zulassung von Phytopharmaka, *pharmaR* 1984, 1, 3, f cited in Hart, 1998b: 175.

<sup>92</sup> Dettling, 2005: 165.

the probability of occurrence, but to the value of the threatened good. *The higher the good at stake, the lower needs to be the probability of causal link to allow for intervention.* In case of high value goods, the mere possibility suffices for intervention.

In the case of uncertainty about damage causes with reference to high value goods (health, life), the principle of “In dubio pro securitate” should apply: the hypothesis of damaging effects should be taken as true as long as no counterevidence refutes it.<sup>93</sup>

The intervention threshold is not only decided upon the acquisition of new data. Also new theoretical insights might contribute to deeper pharmacological understanding and favor or contradict established knowledge about the therapeutic effect of a specific substance.<sup>94</sup>

The mention of “the state of the art of actual research” (“jeweiligen Stand der wissenschaftlichen Erkenntnisse”) as a criterion for deciding drug approvability, recall and suspension, introduces in the legal formulation a second factor of contingency in risk decisions about pharmaceutical products.<sup>95</sup> By means of this formulation, the legislator integrates a dynamic factor in risk regulation and synchronizes safety decisions to scientific developments.<sup>96</sup>

On the other hand, the integration of scientific paradigms in the evaluation of the intervention threshold corresponds to the standardization needs in the field of risk regulation. This has also required an effort towards the systematization of risk knowledge and the gradual reduction of *ad hoc* considerations about single cases.<sup>97</sup>

The conformity to scientific standards for risk decisions is inevitably characterized by the controversies typical of scientific development.<sup>98</sup> In order to account for this fact, the legislator uses the plural form: “wissenschaftliche Erkenntnisse” (scientific knowledges) and thereby allows *any* well-founded suspicion coming from any current of knowledge to require the adoption of adequate countermeasures. The norm is to be interpreted by conforming to the principle of “in dubio pro securitate”:<sup>99</sup> where the vagueness of the term “well founded suspicion” is to be

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<sup>93</sup> Scheu, 2003: 75-78.

<sup>94</sup> See Di Fabio, 1993: 126-127; Räßle, 1991: 90-91.

<sup>95</sup> “Da sich unser Wissen um Risiken permanent verändert, ist jede Bewertung und jede auf ihr basierte Entscheidung unbeständig”: Hart, 1998: 141.

<sup>96</sup> Räßle, 1991: 95.

<sup>97</sup> See Di Fabio, 1993: 111. The traditional basis for police law judgments about danger sources refers to daily experience as a criterion for assessing the probability that damage occurs: this probability refers to the eventuality that no countermeasure is taken in order to contrast the natural course of the events. The criterion of daily experience however, is inadequate to deal with technological danger sources and has been substituted in these fields by the requirements of “technical standard” and/or “state of the art”. The AMG is one of these specific legislation sectors (see also: Räßle, 1991: 93).

<sup>98</sup> Räßle, 1991: 95-96; Kriele, 1976, 355(356); Scheu, 2003: 103.

<sup>99</sup> In the conditions for approval though, the legislator adds to the formulation for benefit proof the expression: “jeweils *gesicherten* Stand wissenschaftlicher Erkenntnisse” (‘established state of the art’: § 25 Abs. 2 Nr. 4 AMG). Procedures to establish efficacy must submit to stricter requirements than criteria for establishing the risk tolerance threshold: See Räßle, 1991: 95-97.

solved by resorting to the interpretation that adheres with the highest fidelity to the spirit and the purpose of the legislation.<sup>100</sup>

### 2.3.2 Tolerance threshold and residual risk

The risk tolerance threshold is the pragmatic answer to ontological uncertainty – risky and beneficial nature of the drug at the same time. The function of § 5 AMG is in fact to prohibit the circulation of drugs not exclusively on the basis of their risk profile, but rather on the combined evaluation of its beneficial and harmful effects.<sup>101</sup>

Given the ambiguous character of pharmaceuticals and the consequent impossibility of absolute safety, the evaluation of drugs cannot result in a distinction between harmfulness and innocuousness but rather between an acceptable (“zumutbar”) and an unacceptable (“unzumutbar”) risk.<sup>102</sup> This is a relational judgment and is done by relating the drug risks to its expected benefit and evaluating them in a comprehensive fashion. The upshot of this evaluation is the classification of the drug as relatively safe or not (“unbedenklich” vs. “bedenklich”) and of the related risks as tolerable or not tolerable (“vertretbar” vs. “unvertretbar”). The evaluation of benefit/risk assessment therefore is the instrument for the acceptability judgment about its damaging effects.<sup>103</sup>

The principle underlying this evaluation refers to the consideration that risks are tolerable to the extent that they are not avoidable for achieving a certain therapeutic purpose. Acceptable is solely the minimal risk compensated by a comparable benefit.<sup>104</sup> The tolerance threshold refers to this comparison and determines the line above which a drug is declared as “bedenklich” (unsafe).<sup>105</sup>

The state’s duty to protect and promote constitutional goods such as life and health finds insurmountable limits in the unavoidably unsafe nature of drug products.<sup>106</sup> Residual risk in general is the risk which cannot be excluded with absolute safety, but which can be regarded as improbable (or insignificant) enough to be considered legally irrelevant. In the case of pharmaceuticals, this is the risk which is to be taken into account in general, independently from concrete signs of damage suspicion.<sup>107</sup>

This has led to the development of criteria for establishing an acceptable level of risk in face of the benefit promised by the health technology, so called *residual risk*.

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<sup>100</sup> Scheu, 2003: 766.

<sup>101</sup> „Funktion des § 5 AMG soll und kann es dabei nicht sein, jedem mit Risiken behafteten Arzneimittel die Verkehrsfähigkeit zu versagen. Eine derartige Interpretation, die den Begriff der Unbedenklichkeit mit demjenigen der Unschädlichkeit gleichsetzen würde, könnte dem ambivalenten Charakter von Arzneimitteln nicht gerecht werden“: Wolz, 1988: 22. „Unbedenklichkeit i. S. d § 5 heißt nicht Unschädlichkeit“: Räßle, 1991: 104.

<sup>102</sup> Räßle, 1991: 50-57.

<sup>103</sup> Wolz, 1988: 83.

<sup>104</sup> Räßle, 1991: 110. Scheu, 2003: 713.

<sup>105</sup> See Krudop-Scholz: 2005: 145.

<sup>106</sup> Scheu, 2003: 725-729.

<sup>107</sup> Scheu, 2003: 708.

This threshold is established through a risk/benefit evaluation, which decides how much risk is to be accepted in the face of how much benefit. It is a relational judgment which determines the legal relevance of a danger and the threshold under which damage caused by endangering sources should be tolerated by the damaged party.

### 2.3.3 Development risk

The combination of the evaluation method based on the risk/benefit assessment<sup>108</sup> with the particular epistemological framework in which drug risks and benefits are learned, i.e. only progressively, makes the approval status unsteady and revocable. Contrary to other fields of safety regulation, in which damage thresholds are generally established in absolute terms, the tolerance threshold for pharmaceuticals varies from product to product and follows the knowledge acquisition related to it. Moreover, differently than from other danger sources (e.g. nuclear power station), where the source of uncertainty is to be traced back to defects caused by human error or technological failures, the danger coming from pharmaceuticals need not consist of a product fault. Health damages are rather the byproduct of an unintended interaction of the chemical entity with the body (drug kinetics and dynamics)<sup>109</sup>, which is not completely foreseeable.

A fundamental concept in this framework is the notion of “Development risk” (design risk). This is the residual risk linked to the *epistemological uncertainty affecting drug also after approval*: a risk which, notwithstanding compliance with the highest safety standards can go undetected for long time after admission into the market.<sup>110</sup> For this type of risk no guarantee of absolute avoidance can be provided even under the best possible preventive measures.<sup>111</sup>

As a consequence, the approval status is unsteady and provisory. New data about the drug coming from the market may change its risk profile and require corresponding measures.

### 2.3.4 Medical criteria for risk acceptability

The reference to medical knowledge as a basis for deciding the tolerability threshold (“damaging effects that exceed the tolerance threshold according to medical knowledge”) is critical point which is object of debate in the legal literature and concerns the criteria for risk acceptability.

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<sup>108</sup> The concept of “Unbedenklichkeit” establishes an inextricable connection between the benefit of a drug and its danger: “Im Gegensatz zum sonstigen (technischen) Sicherheitsrecht, in dem meist (absolute) Schädlichkeitsgrenzen festgelegt werden, stellt der Unbedenklichkeitsbegriff eine Beziehung zwischen dem Nutzen eines Arzneimittels, in der arzneimittelrechtlichen Terminologie der Wirksamkeit, und seiner Schädlichkeit her” Hart, 2004: 467.

<sup>109</sup> Drug kinetics refers to the way the chemical entity is transformed when interacting with the body; drug dynamics refers on the contrary on the action of the chemical entity on the body.

<sup>110</sup> Scheu, 2003: 683.

<sup>111</sup> Dettling, 2005: 164, footnote 18.

Medical sciences can and must offer the preliminary knowledge upon which a risk/benefit evaluation takes place. But their task and competence ends precisely with the description of the risk/benefit situation. Whether the benefit of relieving head-ache justifies the risk of 1: 10<sup>6</sup> agrunolacytosis (changing of blood spectrum) is not a question that can be answered by means of natural sciences: this decision is rather a normative evaluation.<sup>112</sup>

Medical sciences determine the risk/benefit assessment providing the data for decision, but cannot constitute themselves the criteria underlying this decision. The question arises however as to what reference criteria should guide the risk/benefit evaluation and related decision of risk acceptability. The criterion of social consensus proposed by Fülgraff seems to encounter several difficulties, because preference values differ from user to user and from group to group, and therefore a social consensus is difficult to find.<sup>113</sup> Also the reference to the most concerned party and the rule of “hypothetical consent” proposed by Wolz cannot be of any help, for the same reasons.<sup>114</sup>

Hart speaks of a normative consensus in the sense that the decision about risk acceptability is reached through a communication process among the different experts and stakeholders.<sup>115</sup> In this sense “residual risk” is the risk that a society accepts to undergo in exchange for the benefits expected from the danger source.

### 3. Quality, efficacy and safety standards

Drug approval and circulation in the market is determined by quality, efficacy, and safety criteria. The evaluation of these criteria is not only based on scientific standards, but requires the integration of sociological and psychological factors in the experience of illness and risk. This is because the benefit related to a therapy cannot only be measured quantitatively on the basis of organic modifications, but is rather a psychological dimension related to well-being and quality of life improvement as it is experienced by the patient. The same is valid for the evaluation of pharmaceutical risk.

The basis for this evaluation however is a (semi-)quantitative assessment of the objective benefits and risks related to the drug.

From a strictly pharmaceutical perspective, quality refers to the chemical structure, its pureness, and other chemical, physical, and biological characteristics.<sup>116</sup>

Efficacy refers to the statistical significance of its therapeutic effect on the basis of the data coming from clinical studies.

As for safety, it has already been mentioned that absolute risk-freeness cannot possibly be obtained in the case of drugs. The legislator refers to a relational concept of safety, namely “being unobjectionable” (“Unbedenklichkeit”). A drug is declared

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<sup>112</sup> Räßle, 1991: 115.

<sup>113</sup> Räßle, 1991: 114-117; Fülgraff, 1980 “Arzneimittelgesetz” in *Pharm Ind* (42), 581 ff.

<sup>114</sup> See Wolz, 1988: 102.

<sup>115</sup> Hart, 1998b:186. See also Besch, 2000: 61.

<sup>116</sup> Wolz, 1988: 51.

“unobjectionable” (“safe”) when its beneficial effects exceed the risk associated with it. As a consequence a certain amount of risk is taken into account by the legislator and by the risk analyst in connection to the illness risk and the therapy impact. The risk threshold that the society decides to accept for each drug determines its presence in the market. This is normally established by safety regulations and is embedded in a complex system of agencies and stakeholders.

### 3.1 Pharmaceutical benefit

The AMG does not define the notion of benefit. The most commonly cited definition of drug benefit traces back to 1978. It is considered also somehow official, because it was delivered by the president of the BGA (Bundesgesundheitsamt: National Health Office, now BfArM Bundesamt für Arzneimittel und Medizinprodukte) Georges Fülgraff. According to his definition, drug efficacy is *sum of the intended effects in relation to a specific indication*.<sup>117</sup>

A consequence of this construal is that drug evaluation is a relational value proportionally dependent to the severity of the illness which is supposed to cure.<sup>118</sup>

The higher the risk connected to the illness, the higher will be considered the benefit produced by the drug. This is valid also if the drug has only symptomatic effects, when the symptoms of a disease deeply impact the quality of life.

The benefit assessment is related to qualitative and quantitative considerations at the same time: qualitative aspects refer to the therapeutic importance and effectiveness, as well as to the health consequences on an individual and societal level; quantitative aspects are related to the effectiveness probability.<sup>119</sup>

Criteria for judging benefit are:

- Efficacy probability (quantitatively measurable);
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- Efficacy degree;
- Therapeutic importance;
- Healing;
- Life expectancy prolongation;
- Quality of life improvement;
- Symptoms relief;
- Transitory or permanent positive effect.<sup>120</sup>

The efficacy probability is measured by statistical data coming from clinical studies (pharmacological data); efficacy degree refers to the extent to which the therapeutic purpose is obtained; therapeutic importance is a multi-attribute category which involves epidemiological considerations such as the diffusion of the illness in the

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<sup>117</sup> Räßle: 1991: 106-107; Besch: 2000: 56, both with reference to Fülgraff, 1978: 177 ff.

<sup>118</sup> See Räßle, 1991: 108; Besch, 2000: 55.

<sup>119</sup> Besch, 2000: 56.

<sup>120</sup> Hart, 2005: 209; Besch, 2000: 55-56; Räßle, 1991: 107-108; Wolz, 1988: 79.

population, eventual alternative treatments available and their effectiveness, but also the doctor's judgment of the potential impact of the drug; the healing aspect of a drug refers to the degree to which it helps remove the illness (causally vs. symptomatically; directly vs. indirectly<sup>121</sup>); life expectancy prolongation refers to fatal illnesses and the drug contribution in slowing down the course of the illness; quality of life improvement is a multi-scale measure based on quality of life parameters, symptoms relief refers to the extent to which symptoms are removed or alleviated through the therapy; finally, transitory vs. permanent positive effect refers to the drug capacity to remove the illness disturbs only temporarily or definitively.

### 3.2 Pharmaceutical risk

Since the early beginnings of pharmacology, it has always been clear that “poisons in little doses are the best medicines, and useful medicines in big quantities are poisonous”.<sup>122</sup> For instance the efficacy of *digitalis purpurea* against “dropsy”, first discovered by the British doctor William Withering (1741-1799) is due to its enhancing action on the heart contraction power, with consequent water expulsion from the body through the kidney. Its poisonous effect in high doses (delirium, as well as heart cramps up to fatal fibrillation) comes therefore from the same disturbing effect on the heart rhythmus, which in the right dose can be of beneficial therapeutic use for a specific indication.<sup>123</sup>

The so-called “therapeutic range” is one of the criteria to judge the safety spectrum of a drug: up to a certain quantity the drug does not produce any effect (either benefit or damage). It is only from a certain amount that the substance begins to produce an organic reaction, which augments together with higher doses. But from a certain quantity side effects also begin to appear until the point is reached where the drug produces damages. The difference between the minimal therapeutic dose and the damage threshold is called therapeutic range. The therapeutic range of different chemical entities can vary greatly. The *digitalis purpurea*, for instance, has a very limited range: already by double or triple dose, it produces relevant damage to healthy patients. On the contrary, acetyl-salicylic acid begins to produce side effects at five to ten times the normal dose, and can be fatal if the dose reaches 30 to 60 times the normal dose.<sup>124</sup>

The definition of beneficial and harmful effects is not only dependent on the dose, but it is also related to the unpredictability of its impact on the organic system: sometimes unintended effects can result from drug intake, which are eventually considered beneficial for specific disturbances. Therefore unintended effects are not

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<sup>121</sup> The therapeutic function could be indirectly linked to the illness by contrasting some related factor. If medical knowledge point at arteriosclerosis as a plausible/probable cause of heart attack, then for instance, a drug which reduces fats in the blood can be considered beneficial against heart attack: Wolz, 1988: 72; Räßle, 1991: 107, footnote 454).

<sup>122</sup> Verband Forschender Arzneimittelhersteller, 2004: 4.

<sup>123</sup> Ibid.

<sup>124</sup> Ibidem: 5

harmful *per se*. For instance, the lowering of blood sugar level that accompanies an antibacterial therapy with sulfonamides is considered an unintended effect, which can also be harmful in individual cases; however it is a beneficial property in the therapy of diabetes.<sup>125</sup>

Moreover, adverse drug reactions greatly depend from the specific organic and genetic constitution of any single user, so that also a minimal dose can produce side effects (and possibly no benefit). Furthermore in case of pregnancy, the effects of the chemical entity may not be noticed by the mother, but may be of severe consequences for the baby.<sup>126</sup>

If the benefit of a drug can be defined by the sum of intended side effects, then the amount of risk connected to a drug is measured by severity and probability of its *unintended harmful* side effects.

The WHO definition of ADR is: “A response to a drug which is noxious and unintended, and which occurs at doses normally used for the prophylaxis, diagnosis, or therapy of a disease, or for the modification of physiological functions”.<sup>127</sup> This definition excludes adverse events caused by erroneous dosage, administration or prescription, which are called Adverse Drug Events (ADE), and is independent from the mechanisms which produce an ADR. These can be of various nature:

1. pharmacological-toxicological reactions and interactions;
2. reactions depending on the drug mechanisms;
3. pseudo-allergic reactions;
4. allergic reactions depending from the individual immune system:
  - anaphylactic shocks;
  - grippe-like syndromes;
  - damages to the immune system.<sup>128</sup>

1. In the first case the drug components – or a byproduct of the metabolic reaction – lead to a damaging result on a specific organ. The time and dosage associations help identify the drug as a probable cause.

2. In the second case, the same beneficial function for a specific mechanism produces harmful effects on another organ system. An example is the inhibiting

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<sup>125</sup> See Schönhöfer, 1993: 95.

<sup>126</sup> Verband Forschender Arzneimittelhersteller, 2004: 6, 24.

<sup>127</sup> Requirements for adverse reaction reporting, Geneva, Switzerland, World Health Organization, 1975. The definition of adverse drug event has been recently included in the Guidelines for adverse events reporting: [www.who.int/patientsafety/events/05/reporting\\_Guidelines.pdf](http://www.who.int/patientsafety/events/05/reporting_Guidelines.pdf): “An injury related to medical management in contrast to complications of disease” (p. 8).

<sup>128</sup> Schönhöfer, 1993: 96-98. A further classification of ADR is the Rawlins and Thompson’s type A and B categorization. Type A are ADR which are doses-dependent, causally connected with the drug components, and therefore also predictable and identifiable as such. Their severity degree is generally low. Type B ADR are doses-independent, unavoidable reactions with no predictable connection with the drug. These are generally characterized by high severity and irreversible damage (e.g. anaphylactic shock). The severity of an ADR can be judged through the degree of impairment of normal activities up to fatal events.

effects on prostaglandins production induced by anti-rheumatic drugs. This inhibiting effect favors the anti-infectious action, but at the same time damages the stomach mucous membrane, where prostaglandins protect the mucosa from self-absorption. The link between unintended and intended effects is direct and follows from the same mechanism.

3. By pseudo-allergic reactions the drug components affect directly the regulating processes which influence the immune-system. Also here the causal attribution is eased by direct proportionality to dosage and by the time association.

4. Real allergic reactions though are neither dosage dependent nor timely associated with drug intake. Apart from anaphylactic reactions, which take place soon after the drug has been ingested, grippe-alike reactions or damages of the immune system through pharmaceutical components are very difficult to recognize as such.<sup>129</sup> This is due to the lack of any time or dosage association, and to the similarity of the symptom to warning signs for an illness (sometimes the same which is being treated!). Allergic reactions are very deceptive and therefore often lethal.

The definition of risk traditionally provided by safety regulations is derived from a multiplication of the two dimensions of damage *severity* degree and *probability* of occurrence,<sup>130</sup> where the damage is any injury caused to goods protected by the law.<sup>131</sup> In analogy to the benefit assessment, a quantitative measure (occurrence probability) should weight a qualitative factor made up of several dimensions (severity degree). The evaluation of risk related to a drug in the risk/benefit assessment prior to market approval is made along the following categories:

- Frequency (risk probability: quantitative measurable);

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- Severity, intensity, extension, duration (risk magnitude);
- Type and severity of impact on life quality
- Controllability
- Reversibility
- Possibility of recognition
- Possible countermeasures.<sup>132</sup>

Similarly to the benefit assessment, the major difficulties lie in the operationalization and standardization of these parameters. Generally the hypothetical impact on autonomy and work capacity is the standard criterion taken into consideration in evaluation algorithms together with the level and range of medical countermeasure

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<sup>129</sup> Grippe-alike syndromes are characterized by phenomena which are typical of flu: fever, head-ache, feebleness, muscle and articular pain. This illness was at first named "serum-illness" because it was often observed after administration of diphtheria-sera. Damages to the immune system, typical of the third type of allergic reactions, consists in the functional deviance of defense cells, which attack and destroy body's own structures because they mistake them for foreign formations. Schönhöfer, 1993: 97-98.

<sup>130</sup> Besch, 2000: 56; Räßle, 1998: 108.

<sup>131</sup> Räßle, 1991: 49.

<sup>132</sup> Hart, 2005: 209; Besch, 2000: 56; Räßle: 1991: 109.

needed to contrast it. For very severe side effects irreversibility of damage up to fatality are the extreme points of the scale.

### 3.3 Risk-benefit assessment and evaluation

The condition for market approval is a positive risk/benefit assessment in absolute terms (when no other drugs compete with the candidate in the market) as well as relative to the pharmaceutical environment (i.e. in relation to treatments already present in the market for the same indication).<sup>133</sup>

This evaluation is based on a comparative weighting of therapeutic importance and efficacy on one side, and of risk severity and frequency on the other side (according to the principle of inverse proportion: the higher the risk, the lower the probability of its occurrence has to be).<sup>134</sup> It is a risk-risk evaluation where the health consequences of different alternative treatments need to be compared and evaluated in face of the illness health implications.<sup>135</sup>

At any rate for an r/b assessment to be positive, the risk-“sum” associated to the product must be inferior to the risk-“sum” associated to the illness, or to the other products in relation to the benefit.

Given the relational value of the benefit in relation to the illness severity, and of the relational weight of the risk in relation to the benefit, the principle underlying risk/benefit assessment translates in an optimizing rule, precisely of reciprocal optimization.<sup>136</sup>

When fatal consequences on both side of illness and drug are under consideration, then the comparison can be reduced to a numerical difference:

Benefit/risk assessment	Case
negative	Illness X is fatal in 10% of the cases. Drug Y cures the illness in 95 % of the subjects but can produce fatal ADR in 6% of them.
“undecided” → negative	Illness X is fatal in 10% of the cases. Drug Y cures the illness in 95 % of the subjects but can produce fatal ADR in 5% of them.
positive	Illness X is fatal in 10% of the cases. Drug Y cures the illness in 95 % of the subjects but can produce fatal ADR in 4 % of them.

Relative assessment:

Benefit/risk assessment for Z in relation to Y	Case
Negative	Illness X is fatal in 10% of the cases. Drug Y cures the illness in 95 % of the subjects but can produce fatal ADR in 1 % of them. Drug Z cures the illness in 95 % of the subjects but can produce fatal ADR in 4 % of them.
“undecided” →	Illness X is fatal in 10% of the cases.

<sup>133</sup> See a. o. Hart, 2005.

<sup>134</sup> Nell, 1983:124

<sup>135</sup> The multiplication formula “severity x probability” which is inherited from danger avoidance regulations (severity of danger x probability of occurrence) is not dispensed from critics. In fact it is the absolute value of the endangered good that should be considered rather than the possible damage dimension: Dettling, 2005: 164, who also cites Di Fabio, 1994: 54 and Stoll, *Sicherheit als Aufgabe von Staat und Gesellschaft*. 2003: 152ff, 167 ff, 434.

<sup>136</sup> Hart, 2005: 209.

positive	Drug Y cures the illness in 95 % of the subjects but can produce fatal ADR in 1 % of them. Drug Z cures the illness in 95 % of the subjects but can produce fatal ADR in 1 % of them.
positive	Illness X is fatal in 10% of the cases. Drug Y cures the illness in 95 % of the subjects but can produce fatal ADR in 1 % of them. Drug Y cures the illness in 95 % of the subjects but can produce fatal ADR in 0.9 % of them.

On most occasions though, comparison is made difficult because of the diversity of drug effects: these can be limited to inhibiting or symptomatic functions, and the illness itself can have other consequences than death if not treated. For these cases additional aspects need to be used. However, the epistemological difficulty lies here in the parameterization and quantification of these positive and negative health factors. Moreover, for each drug there is a different combination of values for the several parameters. The table presents a hypothetical comparison between two drugs (X; Y) with same indication:

**Comparison table between two hypothetical drugs (X, Y)**

Benefit parameters	drug	
	X	Y
Efficacy degree	.9	.9
	0	5
Therapeutic importance	8	7
Healing	6	6
Life expectancy prolongation	9	9
Life quality improvement	7	8
Symptoms relief	8	9
Transitory vs. permanent positive effect	p	p

Risk parameters	drug	
	X	Y
Frequency (risk probability)	.0	.0
	1	1
Severity, intensity, extension, duration (risk magnitude)	8	8
Type and severity of impact on life quality	7	9
Controllability	2	3
Reversibility	no	no
Possibility of recognition	2	1
Possible countermeasures	4	3

The evaluation of all parameters in the comparison of different drugs determines a complex configuration: for each treatment, the combination of parameter values is diverse. The assessment would be easy if only one of the factors considered would differ, or when opposing divergences would differ strikingly in quantity: such cases are very rare.

Major difficulties in the risk-benefit assessment and evaluation task can be summarized under the following points:

- 1) The quantification of some factors is especially difficult to establish (e.g. Life Quality);
  - a. The scientific knowledge upon which the assessment should be made is heterogeneous and not rarely controversial;<sup>137</sup>
  - b. The preference values associated to these factors may differ from group to group of stakeholders with consequent variance of risk acceptance;<sup>138</sup>

<sup>137</sup> Räßle, 1991: 96.

<sup>138</sup> See Hart, 2005; 2004; 1998; 1998b.

- c. Risk exposure is also different for each user depending on drug sensitivity;
- 2) As a consequence, no standardized operationalisation of these parameters has taken place.<sup>139</sup>

Statistical data about efficacy and risk therefore constitute only a part of the risk-benefit assessment. The pharmacological data must be further evaluated in the perspective of relevant health issues. On the basis of the risk/benefit assessment, performed by pharmaceutical and medical experts, a risk/benefit *evaluation* is issued, upon which the authority decides in favor of the drug approval, and other safety interventions.<sup>140</sup> However, even if the two tasks of risk/benefit assessment and evaluation should be performed officially by experts and the authority respectively, both are strictly intertwined.<sup>141</sup> It is a communication process which takes place among the diverse stakeholders.<sup>142</sup>

The uncertainties at the assessment level transfer to the evaluation level.<sup>143</sup> Safety (“Unbedenklichkeit”) and benefit remain vague legal terms which need specification through the cooperation of different stakeholders (experts, pharmaceutical companies, administrative authority) within a procedural and evaluative legal-scientific/theoretical-practical perspective.<sup>144</sup>

### 3.3.1 Risk exposure

For obvious reasons, the risk benefit assessment and evaluation cannot be tailored to each single eventual user. It is rather a general judgment on the basis of the entire population of patients considered as a whole.<sup>145</sup> Some severe risks might therefore constitute no barrier to drug approval if their statistical weight is deemed to be irrelevant.

The most striking consequence of the general character of risk/benefit evaluation is that *some users might be concerned by side effects which are intolerable per se in comparison to the indication*. This is possible because even if these side effects are severe, their low probability incidence acts as a compensatory weight in the evaluation of the drug (they are multiplied by a low probability incidence): as a consequence, the drug is approved for the market notwithstanding.

The disappointing corollary is that in individual cases the use of the drug might result in damage which is worse than the illness condition. This eventuality cannot be avoided in the case of mass products distributed among a heterogeneous population.<sup>146</sup>

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<sup>139</sup> Besch, 2000: 55. See also Hart, 1998b: 185, footnote 39 and Räßle, 1991: 113-11

<sup>140</sup> Wolz, 1988: 101; Besch: 2000: 54.

<sup>141</sup> Wolz, 1988: 102.

<sup>142</sup> Hart, 2004: 204.

<sup>143</sup> Wolz, 1980: 104.

<sup>144</sup> Francke, Hart, 1999: 83.

<sup>145</sup> Scheu, 2003: 714

<sup>146</sup> „Zu viel oder zu wenig Schutz einzelner Verbraucher ist wegen der heterogenen Zusammensetzung der Gesellschaft unvermeidbar“ Wolz, 1988: 23. As it will be shown in the second chapter, compensation norms are precisely established in order to face these unfortunate events.

A crucial factor in this sense is a deeper knowledge of risk groups. If it can be established that particular groups are more subject than other to be affected by certain side effects, than a special risk/benefit assessment should be made for this group, and for the rest of the population. The two assessments could lead to precautionary warnings for the more sensitive group, or to exclude this group from usage (contraindications).<sup>147</sup> But more importantly this could help the doctor assess more specifically the kind of risk his patient is exposed to.<sup>148</sup>

The peculiarity of organic reactions to a drug should indeed lead to a more differentiated approach to drug authorization, so that the health of the majority would not prevent a particular group to profit from the drug. In fact the risk/benefit assessment of a drug might be generally negative, but specifically positive, if a special subgroup of users is taken into consideration.<sup>149</sup> Both safety and efficacy would profit from a more refined approach to drug approval.

### 3.3.2 Preference values

The impossibility of finding a mathematical standardization for the comparison of all risk and benefit factors is also a consequence of the fact that their assessment and evaluation needs to be performed on the basis of preference values. However, in that this assessment cannot but be general, personal preferences are necessarily taken into account only by means of a compromise. The legislator has granted the medical sciences a direct voice in the decision of risk acceptability, less clear is the role of doctors' and end-users preferences in the establishment of the acceptability threshold through risk/benefit assessment.<sup>150</sup> In this respect, the principle should be that of "hypothetical consent": the evaluation of parameters which are not quantifiable is to be based on what can be considered reasonable for the most directly concerned party (the drug users).<sup>151</sup> However, the extent to which this principle can be implemented is all but established.

This state of affairs has resulted in the gradual acknowledgment, at least in the legal literature, of a decision space in which epidemiological data and their medical

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<sup>147</sup> Hart underlines this point and speaks in favor of a diversification of risk strategies according to different risk groups: This could be a solution in cases where different benefit and risk profiles in the drugs which are compared can constitute dilemmas for approval. If, for a definite group, a specific drug minimizes the risk and optimizes the benefit in comparison to other treatments, then this should be approved to the market for that group (Hart, 2005: 211-212).

<sup>148</sup> Wolz, 1988: 90-91.

<sup>149</sup> Hart, 2005: 212.

<sup>150</sup> For Hart the preferences of the medical professional are indirectly acknowledged through the reference to medical sciences throughout drug safety regulation norms. However he also notes that the choice made by the single doctor is narrowed down to the drugs approved for market circulation: in this sense their risk acceptance level might be disregarded on a practical level. As for direct consumers, the indirect proof of considerations of their risk acceptance level in the risk/benefit evaluation may come from some approval decisions such as the admission of Viagra into the market. The side-effects of this drug are from a mere medical perspective not counterbalanced by an equivalent therapeutic value. It seems then that the approval decision has resulted from the consideration of other, principally user oriented, aspects (so called "life-style" drugs). Hart, 2005: 211.

<sup>151</sup> Wolz, 1988, 103-104.

interpretation becomes integrated through a communication exchange among the different stakeholders.<sup>152</sup> In this perspective, risk decisions are the result of a “normative consensus”, where the level of risk acceptability is determined socially and by the different concerned parties.<sup>153</sup> This decision margin left to social instances grounds the base for a political element in drug safety resolutions.<sup>154</sup>

### 3.3.3 Risk policy

The risk policy determines the level of risk acceptability for drug approval. This means that on the basis of the same risk and benefit a drug can be approved in a system and rejected in another.

Drug approval decisions are never void of risk: both rejection and approval of a certain product bring about potential dangers.<sup>155</sup> The degree of risk avoidance vs. risk proclivity has considerable repercussions on the healing chances for specific patients groups. If conditions for marketing approval are too strict, then important drugs for specific patient groups may never reach the market because they are associated to a level of risk which exceeds the threshold established by the law; if on the other hand, they are too liberal, than the users are exposed to a greater risk (in terms of side effects magnitude and/or probability).<sup>156</sup>

The question here is how much risk the authority *should* and the stakeholders *are willing to* undergo in face of how much benefit.<sup>157</sup>

The decision of a drug approval (or suspension, or recall) thus draws on different competencies and is determined a. o. by the risk acceptance levels of each expert group.<sup>158</sup>

In the USA, for instance, the risk policy has been put into discussion over the last decennials either because of its supposed inertia and over-caution or because of its negligence and carelessness<sup>159</sup>.

These claims reflect the shaky nature of the drug safety status: a status which can legally change after the authority approval, on the basis of risk data coming from the circulation in the market but also depending on the level of risk acceptance.

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<sup>152</sup> See also Besch 2000: 61.

<sup>153</sup> „[ein] Kommunikationsprozess zwischen verschiedenen wissenschaftlichen Disziplinen und Professionen ... Insofern sind arzneimittelrechtliche Sicherheitsentscheidungen auf einen Normativen Konsens ausgerichtet, gesellschafts- und adressatenbezogen und urteilen letztlich über die gesellschaftliche Akzeptabilität von Arzneimittelrisiken“: Hart, 2005: 204.

<sup>154</sup> Hart, 1998b: 187.

<sup>155</sup> Scheu, 2003: 725

<sup>156</sup> The same problem is only deferred but not removed through the adoption of suitable mathematical models as an instrument for establishing and legitimizing a defined risk policy (see Wosniok, 1996: 29 ff).

<sup>157</sup> Hart, 2005 210.

<sup>158</sup> Hart, 2005: 210-212.

<sup>159</sup> See, Rubin, 2000; Hansen, 2000.

### 3.3.4 Risk acceptance

The political character of drug safety decisions was the object of a debate in Germany at the end of the '70s.<sup>160</sup> The two poles of the debate advanced arguments pro and contra the legitimacy of the integration of social risk acceptance criteria in the acceptability judgment for drug approval and circulation in the market. Hart identifies in the work of Di Fabio the consequent development and upshot of this debate. Following Di Fabio, terms such as benefit and risk are purposely left vague by the legal system.<sup>161</sup> It is precisely by integrating lay risk perception and the different concepts of risk pertaining to different disciplines that risk/benefit optimization can improve methodologically.<sup>162</sup>

Furthermore, other disciplines specialized in the investigation of risk, other than medicine, might help optimize the risk/benefit evaluation methodology, in that they provide important insights on diverse dimensions of risk. These studies range from the empirical work of Paul Slovic and colleagues to the sociological considerations of Niklas Luhmann.<sup>163</sup>

Following socio-psychological research on risk perception, several dimensions can be accounted for to explain the level of risk acceptance. Considering these dimensions, a divergence in risk acceptance attitudes can be identified between lay and expert or decision-makers.<sup>164</sup>

Dimensions like voluntary exposition, control, expertise are generally linked to risk proclivity. Also the membership to an institution/organization and the associated sense of responsibility distribution is also connected with proclivity to risk. As a consequence, both the authority and pharmaceutical firms – as expert and complex institutional/organizational entities with decision making powers – tend to set the acceptability threshold lower than a lay decision maker would do. The legal level of drug risk acceptance is therefore “structurally” lowered in comparison to the lay level of acceptability. This demands a counterforce to balance the risk proclivity of administrators and pharmaceutical entrepreneurs.<sup>165</sup> Actual drug regulation does not provide any substantial means for the involvement of the public or target groups in drug risk policy and decision making.

Legal and political arguments speak for the citizen's involvement in the decision processes related to health provision and safety system, as well as to the establishment of quality standards and to the organization of the health care system in general. The regulation system however lacks the adequate law instruments to allow and promote participation.<sup>166</sup>

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<sup>160</sup> See Hart, 1998b, 188.

<sup>161</sup> Hart, 1998b: 188. The reference is to Di Fabio, 1994 and 1993: 109, 130 f.

<sup>162</sup> Hart, 1998b: 188-9.

<sup>163</sup> Hart, 1998b 182, 188-93. See paragraph 3.3.4.

<sup>164</sup> Hart 1998b: 190 ff.

<sup>165</sup> Hart, 1998b: 193, 202.

<sup>166</sup> Francke, Hart, 1999: 207.

#### 4. Safety regulation after approval: Risk management and Development risk

Because any drug can be affected by risks which go undetected at time of approval, there is the possibility that the drug reveals itself as unsafe (“bedenklich”) when already in the marketing phase. This theoretical possibility is captured by the notion of development risk and is dealt with by resorting to a risk prevention system.

Whereas classical danger avoidance is rather reactive and casually prompted by the single hazard, the drug risk prevention system is characterized by a systematic surveillance and pervasive regulation of all phases of risk management.<sup>167</sup>

Thanks to harmonization efforts such as the International Conference for harmonization (ICH), aimed at standardizing the approval conditions among USA, Japan, and Europe,<sup>168</sup> approval, registration and surveillance of pharmaceuticals follow a standardized procedure which is relatively homogeneous across countries, and can be broken down into the following phases:

1) Application for marketing approval: The pharmaceutical firm applies to the competent Authority for a New Chemical Entity (generally already patented in this phase): data consist mostly of “in vitro” studies and animal trials.

2) Clinical trials (in three phases): designed to prove efficacy and safety of the new chemical entity: first on a delimited number of healthy volunteers (to prove safety), then on a greater number of possible patients (to prove efficacy and further confirm safety), finally on a large scale – 300 to 1500 trials – (to further confirm both variables)<sup>169</sup>.

3) Post-market surveillance: At the stage of approval, too little is known about the remotest side-effects (those occurring in one out of 10.000 – 20.000 cases).<sup>170</sup> These are also the most severe (sometimes with lethal consequences) and most difficult to identify because of the complex causal network in which they are embedded.

The knowledge about a newly approved drug is therefore severely limited. Some even speak of population experiments.<sup>171</sup>

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<sup>167</sup> Di Fabio, 1993: 120.

<sup>168</sup> See: [http://www.ich.org/UrlGrpServer.jsr?@\\_ID=276&@\\_TEMPLATE=254](http://www.ich.org/UrlGrpServer.jsr?@_ID=276&@_TEMPLATE=254)

<sup>169</sup> Schönhöfer et al. 1998: 110. Clinical trials are subject to a detailed legislation concerning among other ethical issues related to human experiments: Both FDA and European Guidelines as well as the German national legislations require compliance to Good Laboratory Practice Regulations. In the USA they have been introduced in 1976. In Europe they draw back officially to 1979: 79/831/EEC (generic safety trials requirements to GLP compliance). A widespread GLP application is mainly due to the directives 88/320/EEC (Jun. 9 1988), 90/18/EEC (Dic. 18 1989). In Germany, compliance to GLP is explicitly required by § 40-42 AMG; in Switzerland by § 53-57 HMG. In Italy, besides a 1967 circular of the Direzione Generale del Servizio Farmaceutico, which only mentions GLP, compliance norms have been introduced only 1992 by the decree n. 120 (Jan. 27) – as application of the above mentioned European directives (information source: Ministero della Salute: <http://www.ministerosalute.it/faqGenerale/faqGenerale.jsp?id=36&area=professioni&paginaprovenienza=nuovo&numeroFaq=6#6>).

<sup>170</sup> The detection limit for side effects rests with one case out of 1000 (Verband Forschender Arzneimittelhersteller, 2004: 15).

<sup>171</sup> “Bei der generellen Verwendung nicht ausreichend geprüfter Medikamente handelt es sich um kontrollierte Bevölkerungsexperimente – während die Patienten davon ausgehen, mit wirksamen und sicheren Medikamenten behandelt zu werden.” Berger, Mühlhauser, 2000: 155. Generally, important information both about drug benefits and risks can be acquired only through structured post-authorization studies (§§ 28 IIIa, 67 VI AMG) and risks comparisons.

In order to face the problem of unexpected adverse reaction, a post-market surveillance system is established as a monitoring and alarm device to manage pharmaceutical risks. Cases of side-effects are spontaneously communicated and periodically collected so as to update the drug profile and take adequate and timely countermeasures in case of risk suspicion.

The double safety control system provided by AMG comprehends therefore not only a selection gate prior to approval, but also a risk management system after the product has entered the market. This is intended to avoid or reduce the risks arising from any lack of information at time of approval (epistemological uncertainty).

The risk management system is based on a surveillance system (§§ 64-69a) and develops in the following phases:

- drug monitoring and risk data recording (risk information gathering);
- risk analysis;
- risk evaluation;
- risk decision.<sup>172</sup>

#### **4.1 Drug monitoring**

Post-marketing drug monitoring presupposes a system of information exchange.<sup>173</sup>

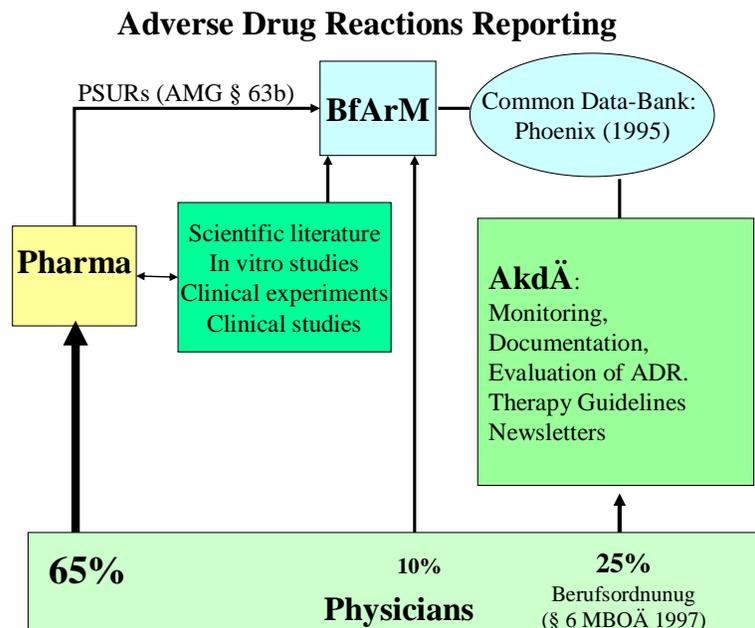
The authority in charge for risk data recording and risk management is according to § 77 AMG the Bundesinstitut für Arzneimittel und Medizinprodukte – BfArM (the Paul Ehrlich Institut – PEI for blood products).

The following chart illustrates the side effect reporting system as it is regulated by § 29 and § 62 - 64 AMG “Stufenplan”, which prescribe among other “Informationsmittel- und wege” (§ 63 AMG).

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<sup>172</sup> Hart, 1998.

<sup>173</sup> Di Fabio, 1993: 115.



**Figure 2 Data Source: Karl-Heinz Munter (1998) and Martin H. Stopp (1998)**

According to § 62, the responsible authority should survey and evaluate all risk news associated with an approved drug as a safety measure for preventing endangering of health and life of humans or animals.

Of course the principal information duty concerns the pharmaceutical firm: when severe or repeated adverse reactions are reported, or interactions with other pharmaceuticals occur, or else the drug reveals to be contraindicated for specific target groups, the firm must notify this to the authority.

Pharmaceutical firms update drug profiles with periodical reports: Periodic Safety Update Reports (PSURs). Since the 14<sup>th</sup> amendment to AMG<sup>174</sup> these are regulated through § 63b Abs. 5 and take place:

- ⌚ Promptly under request;
- ⌚ At least every 6 months in the first two years after approval until introduction into the market;
- ⌚ At least every 6 months in the two years after introduction into the market;
- ⌚ Every 12 months after the following two years after approval (3<sup>rd</sup> and 4<sup>th</sup> year);
- ⌚ In time lapses of 3 years together with the application for approval renewal afterwards.<sup>175</sup>

According to § 29 I the pharmaceutical firm is liable for communicating to the authority any suspicion of a “qualified” risk (for instance severe ADR or interference

<sup>174</sup> In force since 6<sup>th</sup> September 2005.

<sup>175</sup> See, Kroth, 2005: 1433.

with other drugs) within 15 days. Moreover any changes in the documentation related to approval decision must be also notified to the authority.

The Medical Commission for Pharmaceuticals (Arzneimittelkommission der deutschen Ärzteschaft, AkdÄ) acts as advisory committee in the evaluation of the risk/benefit ratio associated with the drug. Moreover it collects all adverse drug reaction (ADR) reports coming from physicians in a data-bank (which since 1995 both AkdÄ and BfArM commonly share).<sup>176</sup>

Also the end-user acts as monitoring “signaler”: in fact, since AMG '94, § 11 I 2 nr. 13 prescribes a specific instruction in the PL so as to invite the drug user to notify to the health professional of any adverse reaction not already contained in the PL.<sup>177</sup>

Risk data is continuously analyzed and evaluated according to the course of action established by the “stages plan” (§ 63 AMG: Stufenplan), which is structured in different procedures at increasing risk degrees:

1. first level: routine sessions: periodical exchange of information;
2. second level: observations and reports about the drug manifest the concrete possibility of risks (danger degree I);
3. third level: extraordinary session – well-founded suspicion of health risks (danger degree II).

The upshot of this process is a decision about the risk tolerability. This can be changed from tolerable to intolerable if it is judged unacceptable in relation to the benefit provided by the product. As a consequence it is declared avoidable, in the sense that the decision maker evaluates that the technology in question can be substituted by other ones, which show a more favorable risk/benefit balance.

If the risk is severe enough to demand for precaution measures but also limited to a specific group, and the drug is important for the community, than *risk communication* can reduce the danger by alerting the more exposed groups.

If the risk regards the entire community, then warning messages help the single users make a personal risk/benefit assessment and decide whether to run the risk or suspend the treatment.

Generally, when a drug is suspected of causing side-effects unknown at time of approval, the authority follows a sequence of steps:

- a. Analysis of post-market spontaneous reports related to the drugs;
- b. Literature review (and/or in-vitro data review);
- c. Risk assessment of alternatives (taking into account drug history and importance to community);
- d. Discussion with the drug manufacturer about the eventuality of providing further studies;

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<sup>176</sup> Additional AkdÄ's tasks are: the issue of therapy guidelines, the publication of an official newsletter (the “Arzneimitteltelegram”) and advisory functions towards the Bundesärztekammer (BÄK) and the Kassenärztliche Bundesvereinigung (KBV).

<sup>177</sup> “Informieren Sie Ihren Arzt oder Apotheker, wenn sie Nebenwirkungen bemerken, die nicht in dieser Packungsbeilage aufgeführt sind”

- e. Consultation of a committee of experts (physicians, medicine academics, pharmaceutical experts);

If the risk is assessed, then (communication) actions follow:

- f. Change labeling ;
- g. Inform the health providers community;
- h. Inform the public;
- i. Suspend the approval;
- j. Retire the product from the market.

The pharmaceutical firm on their turn is granted the opportunity of taking several countermeasures in order to reduce the eventuality of damage:

- Health providers can be warned of possible interactions or contraindications with a “Red Hand Letter” (Rote-Hand Brief) according to § 27 of the BPI Kodex (the auto-regulation code of the Federal Association of Pharmaceutical Companies: Bundesverband der Pharmazeutischen Industrie).<sup>178</sup>
- Other spontaneous actions that the firm can adopt are *product information changing* (by authority received: AMG § 29) and, eventually,
- Spontaneous recall from the market.

The authority obviously has the right to enforce all actions (AMG § 12; 28; 30).

This is a peculiarity which can be considered specific to drug risk prevention norms: in fact the authority is not only entitled to make drug risk information public, but also to enforce warning measures to the responsible firm.<sup>179</sup>

#### 4.2 Causal assessment of adverse drug events

A major problem connected to drug monitoring is constituted by the difficulties related to the assessment of the side effect association with the drug. In fact the data upon which the causal association should be judged are affected by several flaws.

This is a critical issue for risk management interventions, given that they are legitimized by the threshold of well-founded suspicion, which draws the line between monitoring and safety measures.

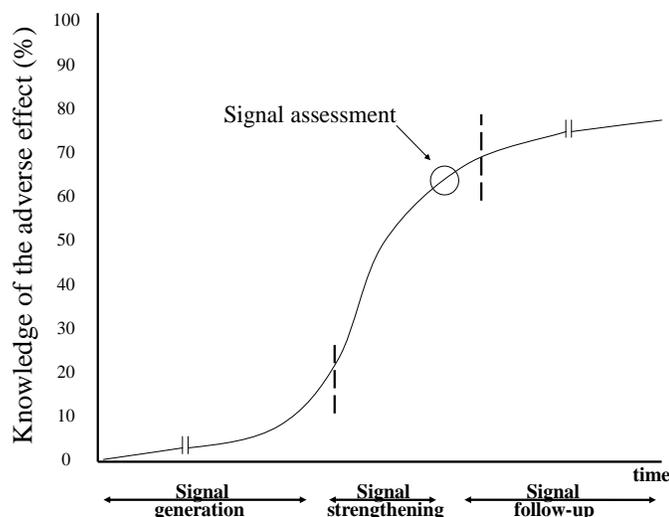
The assessment of a causal link between a drug and a specific side effect after approval can be compared to a signal detection system.<sup>180</sup> First, single cases of suspected association are reported by physicians: at this stage a causal assessment of the single case takes place (signal generation). Through the accumulation of individual side-effects reports, the signal strengthens up to a point where a position about the drug is required. In this phase, interpretation of aggregated data is needed.

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<sup>178</sup> This alarming device consists of indexing an informing letter to the doctor with the message: “wichtige Mitteilung über ein Arzneimittel” under the picture of a red hand. Its origin can be traced back to the Contergan court decision (LG Aachen, JZ 1971, 517. See also Räßle, 1991: 121). See Sickmüller, 1998 for a detailed discussion on the matter.

<sup>179</sup> Di Fabio, 1993: 119.

<sup>180</sup> Meyboom et al., 1997: 376 ff.



**Figure 3: The discovery of an adverse drug effect (source: Meyboom et al. 1997: 376).**

The crucial point in pharmacovigilance is the steep middle part of the curve: this is where a weak hypothesis develops into a strong suspicion and should result in corresponding safety measures. These range from labeling changes to product withdrawal.

Warning measures include: addition of the detected side effect in the information for the doctor (Summary of Product Characteristics, SPC) – and for the patient (PL) – inclusion of special recommendations, and restrictions of the indications for use.

However, it is often the case that regulatory decisions must be made while the scientific proof still need further analytical or experimental studies.<sup>181</sup>

The interpretation of available data takes into account several factors: quantitative strength of the association, consistency of the data, exposure-response relationship, biological plausibility, pharmacological or pathological mechanism, and possible analogies with other drugs.<sup>182</sup>

The aggregated data interpretation is rooted in the causality assessments of the single reports.<sup>183</sup> However these tend to be qualitatively heterogeneous: some provide sufficient documentation to assume a causal relationship; others present instead insufficient or inconsistent information, so that the causal link may even be doubtful or not assessable at all. Therefore, spontaneous reporting databases contain a mixture of signals in various phases of development: probably true and probably false associations, and random associations that may have no pharmacological meaning.<sup>184</sup>

In the attempt to decrease heterogeneity and ambiguity of the data, several methods for assessing adverse medical events associated with drugs were introduced since the early 1980s.<sup>185</sup> Generally they aim at the standardization of the aetiological

<sup>181</sup> Meyboom et al., 1997: 384.

<sup>182</sup> Meyboom et al., 1997: 377.

<sup>183</sup> The causal evaluation of each single reported case is mandatory in many regulations (the German regulation prescribes it under § 29.1 AMG).

<sup>184</sup> Meyboom et al., 1997: 383. See also Hartmann-Besche, 1998: 125.

<sup>185</sup> Meyboom et al., 1997: 375.

procedure through an algorithmic formula.<sup>186</sup> This consists of a series of questions with a numerical score for each answer. The questions regard the time association between drug intake and occurred symptom, disappearance of the symptom with therapy interruption, and other aspects relevant for causality. According to an agreement reached in a meeting in Morges, Switzerland, in 1981, nine points are considered to be the most important in causal assessment algorithms:<sup>187</sup>

1	Drug given to prior event?
.	
2	Reaction at site of application?
.	
3	Drug/adverse reaction interval compatible with the event?
.	
4	Adverse reaction immediately follows drug administration and is of acute onset?
.	
5	Rechallenge positive? (After a repeated exposition to the drug, the AR reappears).
.	
6	Dechallenge positive? (After interrupting the therapy the AR disappears).
.	
7	Were concomitant drugs stopped at the same time?
.	
8	Same adverse reaction to this drug before?
.	
9	Adverse reaction known with the suspected drug?
.	

The scores result in a cumulative value, which is subsequently translated into a ranking category attached to the causality assessment: for instance, ‘unlikely’, ‘possible’, ‘probable’, and ‘certain’. The resulting outcome is not a quantitative measure of the likelihood of causality, but rather a standardization of the uncertainty about adverse reaction causation through semi-quantitative categories.<sup>188</sup>

Regardless of minor differences, the national surveillance systems are generally based on four fundamental criteria: time association (challenge, dechallenge, rechallenge); pharmacology (knowledge of kinetics, dynamics, metabolites, adverse effects) characteristic diagnostic features (clinical data and laboratory results); alternative explanations. Apart from the first one, the judgment of these criteria requires thorough expertise in pharmacology, clinical medicine, and epidemiology.<sup>189</sup>

Particularly, epidemiological information should support one hypothesis rather than another by providing frequency data of symptoms associations (base rate).

<sup>186</sup> One of the most widespread is the Naranjo algorithm, but also the Karch and Lasagna operational method of assessing ADR is used by several companies. Edwards and Lindquist have created a list of quality criteria for causal assessment. Bégeaud et al. have created a method which differentiates among different drugs. See Meyboom et al., 1997, and Buckingham Stevens, 1997 for references.

<sup>187</sup> Meyboom et al., 1997: 377.

<sup>188</sup> However the impact of any question may vary for different adverse reactions. For example, a “positive dechallenge” (prompt recovery after stopping) favors the causation hypothesis, but a negative answer to this question can also be the result of an irreversible side effect, and would therefore introduce an element of ambiguity in the causal assessment system. Meyboom et al., 1997: 382.

<sup>189</sup> Meyboom et al., 1997: 380.

Frequency assessment is in fact complicated by the absence of a reliable base rate: the lack of appropriate consumption data constitute a significant obstacle to the development of an epidemiological analysis. Reference to the turnover produced by a pharmaceutical product is not adequate because it does not correspond to consumption.<sup>190</sup>

The collection of such data is one of the reasons of being of pharmacosurveillance systems, but their spontaneous method constitutes the strongest hindrance to a systematic gathering of epidemiological information. Thus the reporting system cannot be considered statistically flawless.

The risk prevention system is affected by the following sources of uncertainty:

1. The pharmaco-surveillance suffers from “underreporting”.<sup>191</sup> This is due to two interconnected reasons:
  - a. It is fundamentally based on spontaneous reporting (reliability flaw);
  - b. Adverse reactions and illness symptoms are often difficult to distinguish not only for patients but also for physicians (validity flaw).<sup>192</sup> This is due to the complex causal networks linked with the presence of suspicious symptoms.
2. Consequently data are epidemiologic (and therefore statistic-methodologically) flawed.

A further critical shortfall of the standardized methods of causality assessment is that they do not specify the signal threshold, i.e. a criterion for deciding that there is sufficient evidence for a risk management intervention (well founded suspicion). Therefore risk decisions are the result of a shared assessment among different experts within the pharmaceutical company and beyond.<sup>193</sup> This presupposes a continuous communication exchange between company and authority.

Notwithstanding the progress made by pharmaceutical safety regulation in Europe and USA through the emanation of an articulated legislation and the institution of special surveillance agencies, the incidence of drug adverse events is still worrying: it results that in the U.S. 35% of the doctors participating in a survey declared to have observed ADEs in their relatives (7% of which fatal); in England up to 5600 hospitalizations per year are due to ADEs for a cost of € 702 Mio; from a study made in Erlangen (Germany), it results that 3.5% of the hospitalizations are due to ADEs, among which 44% are classified as avoidable. In general the fatality rate of

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<sup>190</sup> „Nur im Rahmen von klinischen Prüfungen steht fest, wie viele Patienten ein Präparat bei welcher Dosierung eingenommen haben“: Räßple, 1991: 109.

<sup>191</sup> “The main limitations are the difficulty in recognizing previously unknown reactions ... and underreporting”: Talbot, Nilsson, 1998: 428. Reasons for underreporting are identified in the following factors: daily work overload in the surgery; fear of own errors; fear of further enquiries; ignorance of the reporting tracks; no availability of reporting forms: Hartmann-Besche, 1998: 124. The problem of underreporting is also mentioned by Di Fabio, 1993: 116; Räßple, 1991: 109; Schönhöfer et al. 1998: 111. Meyboom et al. 1997: 383.

<sup>192</sup> Schönhöfer, P. S., Lelgemann M., von Maxen, A., Wille, H. 1998: 112. Räßple, 1991: 109-110.

<sup>193</sup> See Buckingham Stephens, 1997 for an empirical survey about the causal assessment methods used by different pharmaceutical companies in the U.S.

ADEs is superior to road accidents in USA, England, Norway, Denmark, and Australia as well.<sup>194</sup> According to a report published in the JAMA a good 121 drugs have been retired from the market in the last forty years.<sup>195</sup> If, according to the authors this does not mean a worsening of the safety level in drug approval, still it is no good sign of improvement.

A systematic “intensive” monitoring system<sup>196</sup> and a risk oriented research<sup>197</sup> from side of pharmaceutical companies have been advocated from legal theorists and concerned parties as well. Both at European and national levels, some progress has been made in the management and organization of drug surveillance systems, for instance through reliance on hospitals, rather than only practitioners.<sup>198</sup>

Instead, pharmaceutical research seems to be as much as before oriented towards the prevalent investigation of pharmaceutical benefits. This has not only to do with the low return of investment brought about by research on pharmaceutical risks – a factor that could be steered through tailored economic incentives – but also to do with the structural difficulty of research on side effects.<sup>199</sup> The hypothetical benefit is an identifiable object of investigation when analyzing a specific molecule, the same is not valid for the scrutiny of potential side-effects, which is virtually infinite because it has no definite targets to which it can be referred to.<sup>200</sup>

## 5. Risk communication

A fundamental principle of AMG is the prevention, elimination, reduction, and where this is not possible, the *declaration* of risks.<sup>201</sup>

Pharmaceutical risk management draws on risk communication at different stages and for different purposes. Indeed, risk communication is the key to drug safety.<sup>202</sup>

Given the existential relevance of goods such as health and (physical as well mental) integrity, stronger requirements are demanded of all stakeholders performing information tasks than in other fields of public communication.<sup>203</sup>

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<sup>194</sup> Source: Grandt et al. 2005: 509.

<sup>195</sup> Friedman et al., 1999: 1728.

<sup>196</sup> See for instance Francke, Hart, 1999: 90-91; Schönhöfer et al. 1998: 112 ff.; Hartmann-Besche, 1998: 124 ff.; Stopp, 1998: 102. Grandt et al. also underline that drug monitoring must not only focus on the identification of previously unknown side-effects, but also in the epidemiological task of reliably quantifying the incidence of already known ADRs (2005: 511).

<sup>197</sup> Francke, Hart, 1999: 85.

<sup>198</sup> The “Bremer Modell” must be mentioned among the pioneers of this approach in Germany: see Schönhöfer et al., 1998: 109-120.

<sup>199</sup> Francke, Hart, 1999: 85-86.

<sup>200</sup> Francke, Hart, 1999: 86.

<sup>201</sup> “Tragender Grundsatz des Arzneimittelgesetzes ist die Vermeidung, Eliminierung, Reduzierung und erst, wo dies nicht geht, die Deklaration von Risiken”: VG Berlin (1993) cited in Scheu, 2003: 783.

<sup>202</sup> Scheu, 2003: 714.

<sup>203</sup>“Information ist in aller Regel Bestandteil eines jeden zivil- oder öffentlich-rechtlichen Schuld- bzw. Rechtsverhältnisses. Ihre Erbringung wird allerdings normalerweise in Form einer Nebenpflicht geschuldet. Anders verhält es sich dagegen in sog. Risikoverhältnissen. In diesen bildet die Information einen unverzichtbaren Faktor zur Aufrechterhaltung der Sicherheit der Betroffenen; *sie erstarkt wegen dieser*

Moreover, not only risk communication but also the generation, collection, evaluation of risk information is subject to strict requisites: the standard is provided by the state of the art of medical sciences. This means that the pharmaceutical firm is supposed not only to gather and forward data, but also to get actively involved in research (e.g. through literature review) so as to anticipate as early as possible any drug damage.<sup>204</sup>

Risk communication reveals an indispensable tool especially where a risk/benefit assessment is highly difficult and controversial. If the therapeutic value of a drug is high, the illness severe and no other adequate alternatives are available, so a warning against very severe ADR can constitute an alternative measure to product retirement.<sup>205</sup> Warning actions are the default policy in any uncertain situation involving risk:

“Informational strategy is often viewed as a stopgap measure until the health implications of the hazard are better understood, thus permitting greater flexibility in situations in which our knowledge of risks is evolving over time. In situations in which our knowledge about a risk is not sufficient to warrant a ban but does provide cause for concern, policy makers often adopt *labeling as an intermediate course*”.<sup>206</sup>

The following diagram illustrates the communication flux around pharmaceuticals besides package leaflets and specialist information (SPC for the doctor).

The drug consumer receives information from different sources: the pharmaceutical firm, the doctor and the mass-media. Each source accomplishes different tasks and meets different needs. The PL has a special place among these channels, because it is endorsed by the authority (this is why it is colored in blue) and because it is explicitly proposed as a necessary complement to the therapy.

#### **Pharmaceuticals: Information sources, Channels, and Targets**

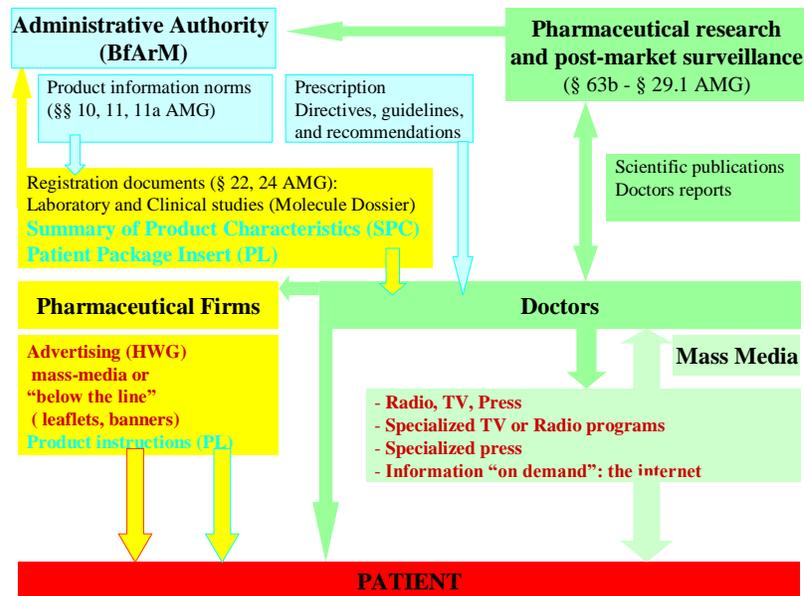
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*Bedeutung zu einer Hauptleistungspflicht in den Rechtsbeziehungen. Das Arzneimittelrecht bildet eines der Beispiele für derartige Risikoverhältnisse.*” Pitschas, 1998: 222 (my emphasis).

<sup>204</sup> Hart, 1998b: 181. See also Scheu, 2003: 769-775.

<sup>205</sup> Hart, 1998b: 177.

<sup>206</sup> Viscusi, Magat, Huber, 1987: 61



**Figure 4: Communication flux around pharmaceuticals**

The two halves of the diagram represent two fundamental aspects concerning risk communication:

- Risk information exchange between authority and experts in the decision phase. In this phase communication aims at increasing the shared knowledge and integrating expertise of different fields and backgrounds. It has fundamentally epistemological aims. The involvement of different stakeholders does not respond to a demand for the largest representation of the public community as a legitimization instrument. It is rather the answer to a complex scientific administrative decision.<sup>207</sup>
- Risk communication to the concerned parties and, when needed, to the public at large, after a decision about the pharmaceutical product has been reached. At this stage of the risk management process, it can either serve as a warning to reduce risk and instruct about adequate use as to prevent avoidable risk, and/or as an instrument for allowing the autonomous decision about the residual risk.<sup>208</sup>

This second aspect concerns the safety of prescription/use and decision autonomy. Prescription safety is proportional to the doctor's acquaintance with the pharmaceutical offer and the risk profiles of the different products in relation to relevant risk groups. To the safety of drug prescription belongs thus also a continuous updating about the pharmaceutical products.<sup>209</sup> On the basis of specialized information – scientific literature, association bulletins, authority newsletters, product information (SPC) – and of medical directives, guidelines and recommendations, the doctor should prescribe the pharmaceutical product which

<sup>207</sup> See Di Fabio, 1993: 123.

<sup>208</sup> Hart, 1998b: 182.

<sup>209</sup> Francke, Hart, 1999: 86.

consents an optimization of the risk/benefit profile in relation to the specific patient. This decision has safety and autonomy components at the same time, because it is ultimately a comparative decision among different products, about the risk which one chooses to undergo in the face of the related benefit.

From the patient's side therapeutic safety depends from compliance to doctor's instructions (therefore indirectly from his knowledge of safety information) but also from a direct involvement in the therapy through control of bodily symptoms and parallel consultation of patient information. PL information represents a privileged vehicle for detailed information from pharmaceutical firm to end-user. However, in that the legal authority validates the product information included in the package, they act as trustees of its quality both for its scientific validity and for its correctness.

The function of product information does not exhaust in its risk prevention function however. In fact, the presence of information about unavoidable risk means that this information is offered to the user in order to let him decide whether to undergo the risk or not based on a personal risk/benefit assessment: directly through the PL, indirectly through the SPC provided to the practitioner.<sup>210</sup>

Given the legal value attributed by safety and liability norms to PLs, the legal function of patient information approaches that of the information provided by the doctor in the institute of "informed consent". As we shall see in the following chapters, in the institutional framework of informed consent, risk communication acquires a specific meaning, precisely that of a liability disclaimer: in case of damage no compensation is guaranteed for residual risk.

Some legal theorist also advances the hypothesis of constructing a special model of informed consent for the pharmaceutical therapy. In this model informed consent proceeds in two phases: first, consent to the prescription after receiving doctor's information, and afterwards, consent to drug intake after reading the PL.<sup>211</sup>

Questions arise however as to the capacity for a lay reader to really deal with such a great amount of specialized information, and ultimately as to the role it plays in compliance problems. In fact, non-expertise in dealing with medical information and other psycho-sociological factors (coping styles to bad news, information seeking behavior) can represent relevant obstacles for a rational risk/benefit assessment and ultimately a real autonomous choice.

## **6. Summary and conclusion**

The pharmaceutical product safety is compromised by several sources of uncertainty. Safety regulation aims to reduce pharmaceutical risk to the minimum while at the same time optimize its benefit. A central tool for this procedure is the evaluation of the drug risk/benefit profile in relation to the indication and to the pre-

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<sup>210</sup> Hart, 1998b: 181.

<sup>211</sup> Koyuncu, 2006: 343 ff. See chapter 4.

existing pharmaceutical environment. Both drug approval and circulation depend on a positive risk/benefit evaluation.

The reference to a risk/benefit profile rather than to absolute safety implicates the acknowledgment that no risk-freeness can be guaranteed for the pharmaceutical product, which is also defined as “unavoidably unsafe”.

Safety regulation therefore concentrates on the aversion of all avoidable risks (through prevention and reaction norms) and in the (penal and civil) sanction of damage.

Notwithstanding all these efforts a residual risk remains, which constitutes a constant danger to private and public health.

Risk communication plays several roles in this framework:

- Given the complex network of competences and expertise involved in the evaluation and surveillance of pharmaceuticals, communication among the different stakeholders is an essential tool for coordinating the different perspectives and activating the most adequate risk management measures;
- In cases where the risk dimension merits alarm but is compensated by a high benefit – for instance, for specific risk groups – warning measures constitute a valid instrument for providing concerned parties with sufficient information to control it (when avoidable) or decide not to undergo it (residual risk).

The autonomy element implicated by this perspective is also underlined by liability law, whose norms regulate the distribution of residual risk. In this respect risk disclosure equates to a discharge of responsibility about risks which are uncontrollable.

As a consequence, the communicative status of PL information is strictly connected to its legal status within this risk prevention and liability framework.

## 2 Product liability

### 1. Liability regimes

As illustrated in the first chapter, drug approval is a provisory administrative act always subject to revision: also after being authorized for marketing, the pharmaceutical product might reveal unexpected damaging properties exceeding its beneficial virtues.<sup>212</sup> The legislator acknowledges this phenomenon by instituting special administrative measures for drug safety surveillance after approval.<sup>213</sup>

In addition to these preventive measures, liability norms for the distribution of damage costs build a complementary tool, which should orient the endangering entity into the adoption of all possible preventative and reactive measures for averting risk.<sup>214</sup>

*Liability in general* should build a complement to the safety system through its steering effect, and *civil liability* in particular should secure the economic compensation for the health impairment suffered by the consumer.

Liability regimes for pharmaceutical products comprise criminal liability and civil liability (tort, strict, and product liability).

- *Criminal liability* is independent from damage and comes into effect for the non-fulfillment of safety norms (§ 95 AMG).
- *Civil liability* presupposes damage. Within civil liability, different regimes are discriminated in relation to the matters of fact presupposed for compensation.
  - tort liability (“Verschuldenshaftung”), regulated by § 823 BGB. It presupposes damage caused by a *breach of professional duty*;
  - strict liability (“Gefährdungshaftung”), regulated by § 84(1) nr. 1 AMG. It does not require breach of professional duty, but that the damage outcome exceeds a threshold level established by the law. Strict liability applies when the damage was not caused by tort (because it was unknown and therefore unavoidable) but it is considered *unacceptable*.

A risk is considered *acceptable (tolerated)* to the extent that no alternative way exists to obtain the related benefit, i.e. to the extent that it cannot be avoided least by

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<sup>212</sup> Besch, 2000: 27, 28.

<sup>213</sup> Sieger, 1989: 1014. See chapter 1, § 4: Risk management.

<sup>214</sup> See Wagner, 2004: 1487 ff. Given that the purpose of this work is the investigation of the legal status of PLs as a preliminary step for the definition of its communicative function towards the single user, I will skip over criminal liability and concentrate on civil liability regulation.

renouncing to the beneficial activity of the related damage source.<sup>215</sup> This is why tolerated risk is also called unavoidable or residual: it is the danger taken into account by the society/the individual in order to profit from the benefits offered by a health technology. It cannot be averted absolutely, but only minimized. Accordingly, risks that can be averted without renouncing the beneficial activity are considered avoidable and therefore unacceptable.

In the case of pharmaceuticals, the acceptability judgment regarding the damage source is the result of a policy decision made within the regulation provided by safety law: a drug may enter/stay in the market until a positive risk/benefit evaluation legitimates it (§ 5 AMG).

The specific norm concerning strict liability for pharmaceutical products is § 84 (1) nr. 1 AMG.<sup>216</sup>

Whenever new risk information is acquired, risks which were previously unavoidable because undetected should be scrutinized in order to decide if they can still be accepted in the face of the provided benefit. Both the authority and the pharmaceutical firm are supposed to react accordingly. Risk-management duties range from product surveillance to additional warning measures up to product retirement. The breach of these duties gives rise to tort liability sanctions.

Strict liability requires that the damage exceeds the acceptability threshold. It does not presuppose a breach of duty, because it covers risks that could have not been possibly averted.

Tort liability is independent from the unacceptability of a risk: any damage is compensated whenever it is not irrelevant and could have been prevented if professional standard duties were adequately met. In this sense avoidable risk is that, whose occurrence is imputable to duty violations and thereby presupposes intentionality or professional negligence.<sup>217</sup>

In general, a risk is considered avoidable if the responsible party should have knowledge of its possible occurrence and has not taken adequate measures in order to avert it. In the pharmaceutical field these are production flaws (pharmaceutical firm responsibility), prescription errors (doctor's responsibility), and consumer misuse (patient's responsibility).

Judicature related to tort liability has established a series of professional duties, the compliance to which presumes the implementation of a risk management system related to development risks.<sup>218</sup>

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<sup>215</sup> See chapter 1 § 2.3.2.

<sup>216</sup> Other norms regulating strict liability in other technological fields are § 25 ff AtomG (nuclear act) for nuclear power stations, and § 32 GenTG (genetic technologies act) for genetic technologies.

<sup>217</sup> Tort liability applies also when the product is not efficacious: the legal motivation is that through the expectations placed in the inefficacious treatment, the consumer is detained from using other drugs present in the market, which are instead efficacious (for the causality requirement, the firm is liable only if other drugs are really available and efficacious).

<sup>218</sup> Hart, 1998b: 180. The first and most detailed sentence in this regard is the Contergan decision. See chapter 1: 4-5.

This chapter and the following illustrate the distribution of responsibilities about pharmaceutical risks among the different stakeholders in order to define the legal meaning of health risk communication and the communicative role of PL as a function of their institutional effects. In particular this chapter is devoted to liability regulation concerning the pharmaceutical firm, whereas the next one will be devoted to the doctor's liability regime.

## 1.1 Tort liability

The German liability system related to pharmaceutical damages comprises a general product responsibility for the pharmaceutical firm and a particular prescription responsibility for the prescribing physician.<sup>219</sup>

Both the pharmaceutical firm and the doctor must respond for civil liability deriving from the violation of legal duties (tort liability). This is regulated by § 823 (1) BGB: "A person who intentionally or by his negligence, unlawfully causes death or injury or impairment of the health, freedom, property is bound to compensate him for damages arising therefrom".<sup>220</sup> According to this norm, compensation conditions for tortuous acts presuppose:

- 1) the existence of a legal duty;
- 2) a breach of the duty (act illegitimacy);
- 3) a damage;
- 4) causal connection between point 2 and 3.

In general the manufacturer of a product has to undertake all possible measures in order to prevent the offence of the consumer regarding any constitutionally protected good, where the level of care is determined by the principle of proportionality: reasonability ("Zumutbarkeit") of required measures in relation to the level of protection demanded by the protected good.<sup>221</sup>

In the case of pharmaceutical firms, given the high value of health as a constitutionally protected good, safety requirements are accordingly strict.<sup>222</sup>

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<sup>219</sup> From the perspective of safety warranty, this dual model has been defined as a "safety regulation system" ("System des Sicherheitsrechts"): Hart, 2003: 603. Doctor's liability regulation is extensively discussed in chapter 3.

<sup>220</sup> English translation from: Dietl, C.E., E. Lorenz, Dictionary of Legal, Commercial and Political Terms (2005). § 823 I BGB: "Wer vorsätzlich oder fahrlässig das Leben, den Körper, die Gesundheit, die Freiheit, das Eigentum, oder sonstiges Recht eines anderen widerrechtlich verletzt, ist dem anderen zum Ersatz des daraus entstehende Schadens verpflichtet". The German formulation differentiates from other European equivalents in that it restricts the general clause to a specific list of goods protected by the constitution (s. Wagner, 2004:1473) and then extends the obligation to compensate to other goods only indirectly in the second paragraph through reference to specific laws (see later on).

<sup>221</sup> Besch, 2000: 79.

<sup>222</sup> Besch, 2000: 80.

The civil duties concerning a product manufacturer concern the following fields of action:

- i. construction (design);
- ii. product manufacturing;
- iii. product instruction;
- iv. product monitoring;
- v. reaction to relevant monitoring data.

i. *Construction.* The product design must meet adequacy and safety standards in relation to the use for which it is marketed. In general, these standards depend essentially on the safety expectations of the consumer and on the state of scientific and technical knowledge. In the case of pharmaceuticals though, the safety level is established through § 5 AMG, and therefore fails to involve the consumer expectations. This is a significant divergence from general producer liability and constitutes a neglect of individual risk acceptance which parallels the similar situation observed in safety regulation.<sup>223</sup>

Damages which are caused by product defects that are not detectable by following the safety standards do not lead to tort liability, because no duty has been breached by causing them (this is covered by strict liability).

ii. *Product manufacturing.* Manufacturing defects are originated by failures in the production process.

Tort liability however, does not cover defects which emerge when the best possible adherence to production standards of quality have been adhered to, because there has been no breach of duty.

Following the same line of argument, so called outliers do not lead to tort liability, because they do arise even in the best possible compliance to production quality standards, therefore they are not the result of a professional duty violation.<sup>224</sup>

iii. *Product instruction.* A product which is not affected by design or manufacturing defects can be considered faulty if not adequately accompanied by relevant warning instructions. These should prevent foreseeable misuse and secure that the product is used without bringing harm to the users or third persons. In the case of pharmaceuticals requirements for warning, instructions have been progressively specified on the basis of important court decisions like the Contergan sentence,<sup>225</sup> the Estil (BGH 11. 7. 1972)<sup>226</sup> and the Asthma Spray case (BGH, 24. 1. 1989).<sup>227</sup>

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<sup>223</sup> Besch, 2000: 81. See chapter 1, § 3.3.4 and related discussion about the neglect of individual risk acceptability in safety regulation.

<sup>224</sup> This differentiates producer tort liability from the liability cases covered by ProdHaftG (product liability law), which also includes outliers.

<sup>225</sup> LG Aachen, 18. 12. 1970 – 4 KMs 1/68, 15 – 115/67. JZ 507 (521).

<sup>226</sup> BGH 11. 7. 1972 (VI ZR 194/70, Stuttgart) VersR, 1972: 1075 (1078).

<sup>227</sup> BGH, 24. 1. 1989 (VI ZR 112/88, Frankfurt am Main) VersR 1989, 399 (401).

It emerges that information duties deriving from liability norms do not perfectly overlap those prescribed by safety norms.<sup>228</sup> Norms such as §§ 10, 11, 11a AMG (product labeling, PL and Summary of Product Characteristics) stipulate necessary conditions for information compliance to legal standards of safety. The adherence to this regulation does not however absolve the pharmaceutical company from tort charges, if it can be established that adherence to these norms was not sufficient to prevent damage and that the firm could have possibly prevented it by adopting additional measures as necessitated by the required level of care. Tort liability for product information is equally regulated by § 84 I 2 AMG. The explicit condition for liability is failure to comply with the state of the art of medical sciences.

iv. *Product monitoring.* As for the duty to monitor the product in the market, this includes the collection of risk data referring to the product as well as to competing products placed into the market after approval. In this sense professional duties linked to product risk management play an incentive role in the detection of development defects. However tort liability does not cover the first case through which the development defect is detected, precisely because it was unknown before.<sup>229</sup>

Also here, the professional standard can be measured along § 5 AMG: this prohibits the marketing of a product whenever there is a well-founded suspicion that the product risk exceeds the benefit. This is the case when other new products which enter the market are less risky, or because new adverse reactions emerge that were not known at time of approval and are considered unacceptable in relation to the benefit or to the risk/benefit balance of other alternatives for the same indication.

v. *Reaction to relevant monitoring data.* As a consequence of this standard, the producer is responsible for undertaking corresponding measures if new data change the product risk profile: changes in design or manufacturing procedures, or additional warnings, up to product retirement from the market.<sup>230</sup>

Tort liability is not only regulated by § 823 I BGB, but also by § 823 II BGB in connection with safety norms. I present § 823 I together with § 823 II BGB for the reader's convenience:

“ (1) A person who intentionally or by his negligence, unlawfully causes death or injury or impairment of the health, freedom, property is bound to compensate him for damages arising therefrom.

(2) The same obligation concerns the person who transgresses a law protecting the good of another. If, according to this law, the transgression is possible also without

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<sup>228</sup> Hart, 1998b: 181.

<sup>229</sup> Besch, 2000: 84.

<sup>230</sup> If no damage (and therefore no tort) results from violations to safety duties, the pharmaceutical firm is nevertheless criminally liable for letting circulate a product which is affected by development risk.

incurring in tortuous acts, the obligation to compensate regards only tortuous transgressions”.<sup>231</sup>

In this case liability is not triggered by the violation of a duty, but by the transgression of a specific norm. Relevant norms in the case of pharmaceutical damages are: § 5 AMG for product safety; §§ 10, § 11, § 11a AMG for product information and § 8 I 1 AMG for product efficaciousness. However no relevant differences derive from the two regimes.<sup>232</sup>

Tort liability does not cover those damages that can emerge unknowingly from the pharmaceutical firm. This potential risk can go undetected for a time sufficient to allow drug approval, and, when realized, cannot fall under tort liability: neither under § 823 I BGB nor § 823 II BGB. It cannot fall under 823 I BGB because the firm has made no illegal act in distributing an approved drug for which no evidence of the risk in question was available until the specific case brought it to light. For the same reason, no violation of a specific norm can be ascribed to the firm, because the damaging product was legitimately circulating in the market until the first damage occurred. The firm would violate the relevant safety norm (§ 5 AMG) only by not retiring the product or undertaking other appropriate measures soon after becoming aware of the risk: yet they can do nothing to prevent the first case of damage occurrence related to it.

Outrageous cases such as the Contergan scandal have made the legislator conscious about the inadequacy of tort liability to deal with these types of product faults (development risk) and ultimately produced the shift from a mere tort liability towards a strict liability regime for pharmaceuticals.

## 1.2 Strict liability

Because of the high meaning of health as a good protected by the constitution, and in consideration of the difficulties experienced by courts in dealing with defective pharmaceuticals only by the means of tort liability, the legislator has introduced an additional form of liability for the pharmaceutical firm in addition to tort liability.

This should constitute a complement to tort liability in cases where no duty violation can be imputed to the firm, but still damages are so relevant that at least an economic compensation is demanded.<sup>233</sup> This has been made possible by introducing the notion of “Entwicklungsrisiko” (“development risk”): with this term the legislator captures defects which are not imputable to negligence by the producer, but must be rather traced back to the epistemic uncertainty inherent to the pharmaceutical product as a consequence of the limited knowledge available at the time of approval.

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<sup>231</sup> “Die gleiche Verpflichtung trifft denjenigen, welcher gegen ein den Schutz eines anderen bezweckendes Gesetz verstößt. Ist nach dem Inhalt des Gesetzes ein Verstoß gegen dieses auch ohne Verschulden möglich, so trifft die Ersatzpflicht nur im Fall des Verschuldens ein.”

<sup>232</sup> See Besch, 2000: 86-88.

<sup>233</sup> Besch, 2000: 30.

Liability for damages not caused intentionally or negligently can be classified as strict liability.

Strict liability has been introduced in pharmaceutical regulation together with the shift from a “danger avoidance” into a “risk prevention” system, through AMG 1976.<sup>234</sup>

The paragraph which refers to strict liability in AMG is § 84 I. It prescribes following conditions for compensation:

The product has been marketed within the norms expressed in AMG, it has caused a relevant health damage, it has been used as determined by its purpose, and in accordance to related instructions, and:

1. *the damage exceeds in a fashion not tolerable the measure established by current medical knowledge;*
2. or the damage could have been foreseen by the producer, and has not been communicated in the medical information or in the patient package leaflet.<sup>235</sup>

This second paragraph is a norm of tort liability referring to product instruction (see § 2 later in this chapter).

As can be noted, § 84 I 1 establishes the same condition for damage compensation which also determines product illegitimacy: trespass of risk tolerance threshold. This means that no compensation is contemplated for damage already taken into account in the risk/benefit assessment related to product approval.

Furthermore, damage whose risk was not contemplated in the risk/benefit assessment prior to approval does not give rise to liability compensation, whenever it does not exceed the tolerance threshold. This tie between safety and liability regulation results in a reduced practical relevance of strict liability. As a preliminary step to the presentation of this issue, two important aspects related to strict liability are presented in the following two paragraphs.

### **1.2.1 The systematization of § 84 I 1 under strict liability**

The legislator explicitly labels § 84 I 1 AMG as strict liability, but there is not unanimity around this classification. Some legal theorists adhere to this categorization,<sup>236</sup> whereas others qualify § 84 I 1 AMG under other sorts of liability.<sup>237</sup>

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<sup>234</sup> For the historical background which brought to the development of strict liability in the pharmaceutical field see Besch, 2000: 28-32.

<sup>235</sup> “Die Ersatzpflicht besteht nur, wenn: 1. das Arzneimittel bei bestimmungsgemäßem Gebrauch schädliche Wirkungen hat, die über ein nach den Erkenntnissen der medizinischen Wissenschaft vertretbares Maß hinausgehen oder 2. der Schaden infolge einer nicht den Erkenntnissen der medizinischen Wissenschaft entsprechenden Kennzeichnung, Fachinformation oder Gebrauchsinformation eingetreten ist”.

<sup>236</sup> Besch, 2000 argues that a violation of a duty presupposes the detection of this duty, and consequently classifies § 84 I 1 AMG as strict liability (liability for a legitimate but dangerous activity): 38.

<sup>237</sup> See Besch, 2000: 36 ff for an overview of different positions in the literature. Hart defines both liabilities for development risk and for instruction defect as objective liability for defective products (“objektive Fehlerhaftung”) (personal communication).

There are in fact some technical difficulties in the straightforward systematization of § 84 I 1 AMG under strict liability. The question can be dealt with by referring to the legal principle underlying the transfer of damage costs from the concerned party to another one. This principle traces back to Roman law and prescribes that *anyone has to bear the consequences of damage insofar as there is no reason to ascribe it to another*. Therefore, compensation rights are linked to liability attribution principles.<sup>238</sup>

The attribution principle underlying tort liability is the illegitimacy of the act which caused the damage; on the contrary strict liability regulates cases where the simple fact of causing the damage gives rise to liability even if the act which produced it is not illegal: in this case the ascribing principle is the *declared dangerousness of the activity* under consideration.

Tort liability is a general norm of civil liability. Strict liability instead is regulated in specific norms for particular danger sources or dangerous activities (nuclear power stations, aircraft services, and genetic technologies a. o.): the risk connected to these activities is taken into account in consideration of the related benefit, but the holder of the activity must respond for any damage caused by it, even if the activity itself is *legally accepted*.

Because the intention of § 84 I 1 AMG is precisely to capture those risks which can go undetected before approval and therefore unknowingly by the pharmaceutical producer until the damage occurs, the consequent responsibility cannot fall under tort liability which presupposes intention or at least negligence, and therefore knowledge of the defect.

However also the classification of § 84 I 1 AMG under strict liability is problematic in that the legislator does not categorize drugs as dangerous products (which should be one of the conditions for subsuming the norm under strict liability),<sup>239</sup> which on the contrary are submitted to an approval procedure prior to marketing, and are admitted to circulate only when declared “safe” (“unbedenklich”).

Instead § 84 I 1 AMG grounds the liability of pharmaceutical producer not generally on the dangerousness of its activity, but on the distribution of concrete defective products.<sup>240</sup> Even if AMG does not explicitly mention defectiveness; still it alludes to it by referring to development and production as possible causal factors for the damage.<sup>241</sup>

In this respect, the marketing of a defective product cannot be considered an “allowed risk”, but, because the production and distribution of pharmaceuticals in general is considered a legitimate activity, § 84 I 1 AMG is also qualified in the literature as liability without fault for product defect (objektive Fehlerhaftung).<sup>242</sup>

The theoretical classification of § 84 II 1 AMG under tort or strict liability is rather a question of legal status and has no actual repercussion in compensation decisions. However the debate around the nature of liability for pharmaceutical development

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<sup>238</sup> Besch, 2000: 33 ff.

<sup>239</sup> Besch, 2000: 35.

<sup>240</sup> Ibid.

<sup>241</sup> Ibid. ff.

<sup>242</sup> See Besch, 2000:37.

risks deserves further attention, and would certainly profit from an epistemological perspective allowing explicitness about the scope and importance of the risk shouldered by the drug consumer.

The liability classification should furthermore do justice to the complexity and uncertainty of knowledge acquisition about a pharmaceutical product by the producer and the scientific community. Most of all it should take into account the general opacity of pharmaceutical products and the *degree of awareness about non-knowledge* on the side of the producer.

### 1.2.2 Residual risk

In order to be approved for the market any drug must obtain approval from the authority. The criterion is established by the law through § 5 AMG, according to which a drug cannot be marketed if there is a well-founded suspicion that it has damaging effects which exceed a tolerable measure as established by actual medical knowledge.<sup>243</sup> The tolerance threshold is established through a risk/benefit assessment as illustrated in chapter 1 and constitutes the benchmark in case of liability resolution. Safety norms and liability regulation are therefore connected.<sup>244</sup> The general consequence of the establishment of a risk tolerance threshold for compensation is the non-applicability of strict liability for residual risk. The table compares the conditions for compensation under tort and strict liability:

		<i>Strict liability</i> § 84 I Abs. 1 Nr. 1 AMG (development risk)	<i>Tort liability</i> § 823 Abs. 1 BGB § 84 I Abs. 1 Nr. 2 AMG
<b>Intolerable damage</b>		Compensation	Compensation
<b>Tolerable damage (residual risk)</b>	Not irrelevant	<b>No compensation</b>	<b>Compensation</b>
	Irrelevant	No compensation	No compensation

Under tort liability any relevant damage raises the right to compensation, when caused by breach of professional duties (construction, manufacturing, instruction, risk management). Instead strict liability gives right to compensation only for damages which exceed the legally tolerated threshold: not the damage alone, but only the negative sign of the risk/benefit evaluation raises liability consequences. Residual risk (below the tolerance threshold) must be shouldered by the damaged party.

This state of affairs is an obvious consequence of the fact that, if, according to safety regulation, the risk is considered tolerable, then, when coming to liability regulation, the legislator cannot consider the pharmaceutical firm liable for this same damage in case of concrete occurrence. The most problematic consequence lies in the fact that any risk associated to an approved drug is by definition tolerable: this means that the

<sup>243</sup> See chapter 1 § 2.3.

<sup>244</sup> Hart; Hilken; Woggan; Merkel, 1988: 160. Also quoted in Besch, 2000: 54.

consumer affected by a risk already taken into account in the approval phase has no right to compensation.

Therefore it can happen that the single user is concerned by a damage which exceeds the personal benefit he derives from the drug and nevertheless cannot claim any right to compensation on the basis of strict liability.<sup>245</sup>

The threshold between tolerable and intolerable damages constitutes a considerable liability limitation in favor of pharmaceutical firms. Only damage whose severity exceeds the legally established tolerance threshold give right to compensation. And, because this threshold refers to the risk/benefit assessment made for drug approval, it tends to be high enough to allow a reasonably loose-fitting selection, so as to permit an adequate drug provision to the market: even very severe risks might have been accounted for in the evaluation phase either because their incidence is very low, or because of the high expected therapeutic effect.

The general risk tolerance threshold will be higher than the individual would allow:<sup>246</sup> questions arise, as to what extent it is legitimate to apply without reservations a general risk/benefit assessment to the single case.

In case of a minor damage, especially in face of a significant therapeutic importance this policy is unobjectionable. However there can be cases where a major damage occurs, which is not compensated by an equivalent therapeutic value.<sup>247</sup>

For instance, given the therapeutic importance of antibiotics, the eventuality of anaphylactic shocks is considered socially tolerable. This is unobjectionable if related to a fatal risk of pneumonia. Still it seems less unproblematic when a mortal adverse reaction to the same treatment is caused within a therapy against a simple cold.

### **1.2.3 Time lapse in tolerability judgment of development risks**

The fact that the market approval conditions and liability duties are based on the same risk/benefit assessment constitutes a tie between the two systems (safety and liability), which raises theoretical and technical problems in the resolution of strict liability conflicts.

In fact even damage whose risk was not known at time of approval does not lead to liability if it would not have brought to a negative risk/benefit evaluation in the case that it were detected before drug approval.<sup>248</sup>

In order to analyze the implications inherent to the legal concept of development risk, legal theorists have investigated the repercussions of pharmaceutical environment evolution in the tolerability classification of damage.

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<sup>245</sup> Erwin Deutsch attributes to this state of affairs the explanation for the fact that very few liability litigations against pharmaceutical firms are raised in comparison to law suits against doctors. Deutsch, 2004: 940.

<sup>246</sup> See chapter 1: 15, 21, 23.

<sup>247</sup> Sieger, 1989: 1015. See the Zycloric case: irreversible hair loss after a therapy against gout: OLG Celle 14. 11. 1984, VersR, 1985: 148-49.

<sup>248</sup> Besch, 2000: 54.

Given that the tolerability judgment is an upshot of a risk/benefit evaluation related to alternative therapies, this evaluation can change from a positive to a negative sign whenever the pharmaceutical environment produces products with a better risk/benefit profile. This means that a damage which would have been tolerated at time  $t_1$ , because no other alternative was available, would be considered unacceptable at time  $t_2$ , because a better alternative exists. The time parameter therefore has a dramatic impact in the evaluation of development risk.

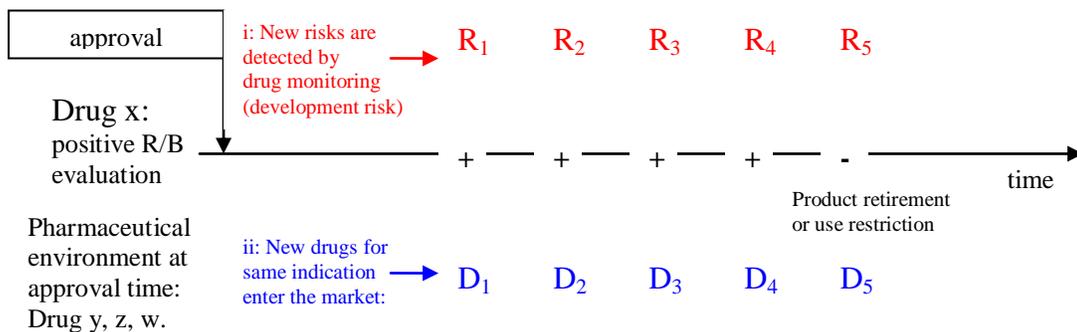
Damage compensation can be obtained only for those damages, which, if known at time of approval, would have changed the risk/benefit assessment from a positive to a negative one and led to refusal of approval.<sup>249</sup>

There is a differentiating point in the judgment about tolerability made in the approval phase and in the litigation context: the time difference between the risk benefit/assessment made in the approval phase and in the litigation can make a difference when new data about the drug profile contributes to change it.<sup>250</sup>

A risk/benefit evaluation can change in time as a consequence of two different types of data:

- i. New knowledge about drug risks (drug toxicity): a drug which is considered relatively safe can, after a certain time, reveal severe side effects which change the risk/benefit assessment from a positive to a negative one;
- ii. New knowledge about benefits and risks of valid alternatives (pharmaceutical environment):<sup>251</sup> a strong drug is tolerated in consideration of a severe illness, but when a new equally effective drug with considerable less damaging effects enters the market, the risk associated with the first one is considered intolerable.

As the graphic illustrates, the risk profile modification of drug x, or of the pharmaceutical environment can change its risk/benefit profile from a positive into a negative one in the course of time:



<sup>249</sup> Sieger, 1989: 1014-1021.

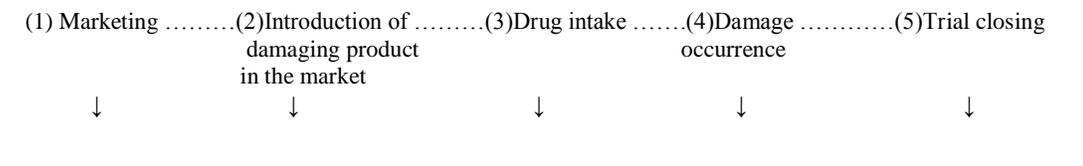
<sup>250</sup> It has also been emphasized that the risk/benefit assessment made in the approval phase mainly rests on medical considerations, whereas in the liability case the judge could take into consideration all instances of the concerned interest groups in his risk/benefit assessment, and therefore in his decision about damage tolerability. Besch, 2000: 61. However, the difficulty affecting pharmaceutical risk/benefit evaluation in general is only augmented by such considerations, and judges do not dispose yet of solid legal categories for eventually justifying the integration of additional parameters into the standard risk/benefit evaluation.

<sup>251</sup> Sieger, 1989: 1016.

**Fig. 1: The two factors influencing tolerability judgment in the course of time: development risk (red) and changing pharmaceutical environment (blue).**

The risk/benefit profile is positive until the well-founded suspicion of an intolerable risk emerges. The tolerability judgment however, is relational and depends both on the risks associated to the drug, and on the risks and benefits associated to alternative drugs for the same indication.

Also when damage occurs, the tolerability judgment must be related to both parameters. The relevant time framework consists however of five possible reference points: drug marketing (erstmalige Inverkehrgabe), time at which *damaging product* is placed into the market (Inverkehrgabe des schadensstiftendes Produkt), time of drug intake (Anwendung), damage occurrence time (Schadenseintritt), closing of the trial (Stand zum Schluß der mündlichen Verhandlung im Haftungsprozeß):



According to the history and systematic interpretation of § 84 I 1 AMG, the relevant knowledge for the judgment of damage tolerability in case of liability trial cannot be the same of drug approval. § 84 I 1 AMG has been precisely introduced to cover risks which were *not detectable at time of approval*, and emerged only in the post-marketing phase.<sup>252</sup> Therefore (1) is excluded.

As for the other points, legal theorists agree that a differentiation should be made between tolerability judgment in relation to the *drug toxicity* (i) and to the alternatives introduced in the *pharmaceutical market* since approval (ii).

For judgments regarding the drug toxicity, relevant knowledge should be the last data available, therefore the knowledge at the time of trial (5).<sup>253</sup>

Legal theorists advance that establishing the same reference point also for the comparative judgment (ii) is counterproductive and legally not justifiable. In this way, pharmaceutical firms would be sanctioned for the very progress to which they collectively contribute. As a consequence innovation would be inhibited and health technology provision hindered.<sup>254</sup>

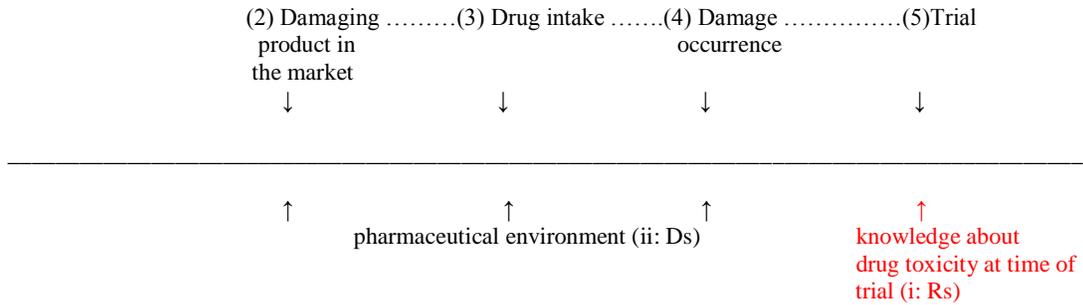
The knowledge about drug toxicity (i) updated to the trial time should be therefore contextualized into an appropriate earlier point in the time framework. On its basis it should be then decided whether, were the new knowledge about drug toxicity available at that time point, the drug would have been judged safe in connection to the related pharmaceutical environment (ii).

<sup>252</sup> Otherwise the only damage that could be taken into consideration would be that already considered at the approval time, and § 84 (1) nr.1 would cover the same liability instances already dealt with by § 5 in connection with tort liability (§ 823.2 BGB). Sieger, 1989: 1016.

<sup>253</sup> Besch, 2000: 67.

<sup>254</sup> See for instance Besch, 2000: 64, and Sieger, 1989: 1017.

Having excluded the time of trial as a suitable reference for the tolerability judgment in comparison to alternative treatments the choice reduces to points 2 – 4:

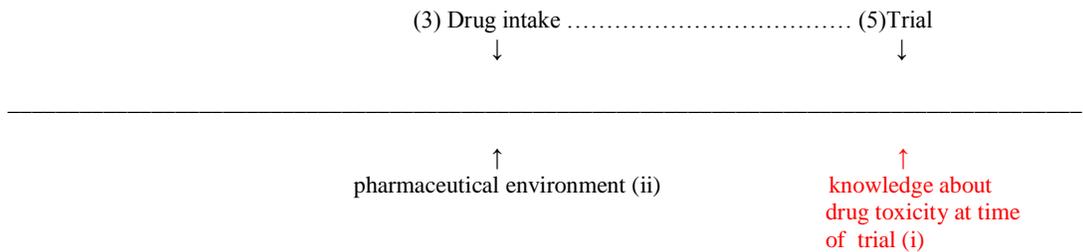


**Fig. 2: Pharmaceutical environment (drugs present in the market: Ds) and enhanced knowledge about drug toxicity (risks: Rs) integrated in the R/B evaluation from different time points.**

The time of damage occurrence (4) can be seldom established with certainty: sometimes the damage arises after long usage or even concerns only the next generation.<sup>255</sup>

As for the notion of “Inverkehrgabe” (2) – product placement into the market – it is so ample that it comprises also the mere storing of products with the intention of marketing it. This means that a great time lapse can pass between the moment when the damaging product officially enters the market and the time at which it is consumed.

Therefore the time of intake (3) seems to be the most suited:<sup>256</sup>



Knowledge about drug toxicity acquired until the last trial examination should be projected back to the time of drug intake and used to make a comparison with the pharmaceutical alternatives available in the market *at that time*. If the resulting risk/benefit assessment is positive, the damaged person has no right to compensation, otherwise if the risk/benefit assessment resulting from this judgment is negative, the risk is considered unacceptable, and consequently the product defective, which leads to liability for the connected damage.

The implication brought about by this analysis emphasizes the gap between drug knowledge at time of approval and in consequent periods. This knowledge gap is accounted for in liability terms by comparing the updated toxicity data with the

<sup>255</sup> Proposed by Rolland: Produkthafungsrecht, § 84 AMG Rdnr. 38 (see Besch, 2000: 65).

<sup>256</sup> Besch, 2000: 64-67.

alternatives offered by the market in the risk/benefit assessment which is specific to the court case.

This is an important progress brought about by the introduction of strict liability in the pharmaceutical field. Still other questions remain unsolved. The most important is the gap between the objective tolerability judgment made for the drug in general, and the specific risk/benefit assessment in the damage situation: as already mentioned, relevant damage may have been taken into account and endorsed in the authorization phase because compensated by a low occurrence probability (and/or by therapeutic importance etc.).

Moreover, the objective risk/benefit assessment and evaluation cannot and does not intend to be tailored to the personal values of the damaged individual. Drug regulation has not found a way to integrate the personal risk acceptance of the consumer in the relevant norms (drug access to the market, product liability). *A subjective evaluation is possible only prior to the therapy on the basis of the information acquired from the physician and the PL.*

### 1.3 Concluding remarks

Liability for the pharmaceutical product damage is principally regulated by tort and strict liability:

- Tort liability concerns tolerable and intolerable damages caused by duties violation of the pharmaceutical firms: construction and production defects, instruction failures, failure to comply to general norms of risk prevention and management (§ 823 I and II BGB; § 84 I 2 AMG);
- Strict liability is limited to intolerable damages (§ 84 I 1 AMG).<sup>257</sup>

Historically liability litigations for health damage against pharmaceutical firms are very few in comparison to the adverse events calculated by epidemiological studies.<sup>258</sup> Furthermore, most of them are raised on the basis of tort liability related to instruction failure. This is due to the difficulties to obtain compensation for damage which does not exceed the tolerance threshold, and to procedural points regarding causal connection to the damage and the burden of proof, which have been however amended.<sup>259</sup>

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<sup>257</sup> It should also be mentioned product liability (ProdHaftG) for cases in which the product is not considered a drug in the sense of § 2 AMG. Also contract liability is at least theoretically possible for instance in the cases where the drug is administered to a hospitalized consumer within a contractual framework where the hospital acts as service provider and pharmaceutical firm at the same time. Besch, 2000: 29. However, these cases are marginal to our line of argument.

<sup>258</sup> See chapter 1 § 4.2.

<sup>259</sup> Since the 12<sup>th</sup> amendment (AMG 2003) it is the pharmaceutical firm that must demonstrate that the damage was *not* caused by the drug, and not the consumer that must prove that it was. Moreover the cause need only to be adequate to produce the damage in question, and its adequacy is judged on the basis of the drug composition, dosage, therapy duration, time association, state of the damaged person at the moment of the intake § 84 (2) AMG: “Ist das angewendete Arzneimittel nach den Gegebenheiten des Einzelfalls *geeignet*, den Schaden zu verursachen, *so wird vermutet*, dass der Schaden durch dieses Arzneimittel verursacht ist. Die Eignung im Einzelfall beurteilt sich nach der Zusammensetzung und der Dosierung des angewendeten Arzneimittels, nach der Art und Dauer seiner bestimmungsgemäßen Anwendung, nach dem zeitlichen Zusammenhang mit dem Schadenseintritt, nach dem Schadensbild und dem gesundheitlichen

A forensic consequence for the relevant difficulties traditionally encountered in obtaining compensation in strict liability litigations against pharmaceutical firms is the prominence of liability suits linked to information duties violation either by the doctor – lack of informed consent/inadequate instruction – or by the pharmaceutical firm – incomplete or inadequate information in the PL.

## 2. Liability for product instruction

Liability for product instruction falls generally under tort liability and is regulated through § 823.1 BGB and § 84 I 2 AMG.

As illustrated for product liability in general, compensation is linked to the tortiousness deriving from the violation of a professional duty which causes damage. Professional duties of risk communication have been gradually established through court sentences, and then stipulated also through safety regulation and liability regulation in AMG 1976 (§ 11, and 84 I 2). However it is only since 1986 that patient information is specifically addressed.

### 2.1 Judicature

As already mentioned in chapter 1, a major contribution of the Contergan decision, was the shift produced in pharmaceutical safety regulation from “danger avoidance” to “risk prevention”.<sup>260</sup> However, this sentence is important not only for having specified important aspects of strict liability, but also for stressing the illegitimacy of incomplete risk information as an offence to freedom rights, such as the right to autonomous decision about therapeutic risk.

In fact, the Contergan decision greatly emphasizes the importance of risk communication both as a prevention tool and as a guarantee for the right to decision. In the inventory of general consumer protection duties, the Contergan decision includes and legally grounds specific *risk disclosure duties*.

The responsibility to inform the consumer derives from the established or presumed dangerousness of the pharmaceutical product and the consumer *right to decide*, whether to undergo the risk connected to it or not, in face of the expected benefit. The Contergan justice explicitly parallels these risk disclosing duties to those concerning the doctor and steadily confirmed by court decisions since the end of the XIX century.<sup>261</sup> The doctor duty to inform the patient derives from the violation of bodily integrity implicit in any medical intervention, the illegitimacy of which is removed through prior adequate information. The same considerations are valid for the producer of a product which causes health damage to the user.

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Zustand des Geschädigten im Zeitpunkt der Anwendung ... Die Vermutung gilt nicht, wenn ein anderer Umstand nach den Gegebenheiten des Einzelfalls geeignet ist, den Schaden zu verursachen...” (my emphasis). The reversal of the burden of proof and the introduction of the adequacy theory of causality are the result of a long debate generated by a second health catastrophe produced by blood transfusions of HIV infected blood. See Rehman, 2003: 465-66, 473-474; Besch: 2000: 32, Besch (2000); Kullman (1995).

<sup>260</sup> LG Aachen, 18. 12. 1970. See chapter 1 § 2.

<sup>261</sup> See chapter 3 for a detailed discussion.

The court decision adds also that the right to decide about one's bodily integrity is not only violated when the information failure relates to a proofed risk. Already by danger suspicion the user is concerned by the decision whether they want to *risk* health impairment. This autonomy right entails a risk disclosure duty by the firm.<sup>262</sup>

The risk disclosure duties obviously regard also prompt and adequate communication towards the health professional, in that they take on damage responsibility through the prescription of a certain drug, and also because they are on their turn obliged to disclose medical risks related to the therapy.<sup>263</sup> The pharmaceutical firm must inform clearly and in a comprehensible fashion, about the dangers connected to a drug, so that doctor and patient can decide whether and to what extent they want to dare the use of the product.<sup>264</sup>

Also the risk disclosure threshold is decided from case to case through the above mentioned criteria.

The sentence makes clear that pharmaceutical warning aims not only to avoid risk (safety), but also to guarantee the right to self-determination. This is the result of the unavailability of residual pharmaceutical risk. For risks that are inherently associated to drug usage, and cannot be avoided through adequate precautions, information serves the purpose of allowing the consumer to decide whether to undergo them or not in exchange for the promised benefit.

A second milestone in the history of pharmaceutical information regulation is the Estil sentence (1972).<sup>265</sup> This decision takes the opportunity of a damage case caused by insufficient warning in order to specify with more detail the information duties that the pharmaceutical firm must fulfill.

The Estil case relates to a severe infection with consequent limb loss, caused by an erroneous arterial injection of a narcotic. The arterial injection constituted a misuse of the narcotic drug, which should have been instead injected through the vein. Nevertheless the pharmaceutical firm, and not the doctor, was held responsible for the damage, because of insufficient warning.

The judgment was based on considerations related to the probability and health implications of medical error, and the awareness about it by the pharmaceutical firm (tortuousness). The justice remarks that it was an acknowledged fact among health professionals that, by an elbow injection, the inoculation of the Estil narcotic into an artery instead of a vein could not be excluded with certainty. Given the predictability of this fault, the severity of its consequences, and the specificity of this danger, the pharmaceutical firm should have adequately emphasized the risk of an arterial injection, and explicitly mentioned the consequences of this kind of misuse. The simple warning to avoid an artery injection is not considered sufficient because it

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<sup>262</sup> "Das Recht des Patienten oder Arzneimittelverbrauchers, über Eingriffe in seine körperliche Unversehrtheit zu entscheiden, wird aber nicht erst dann berührt, wenn die schädliche Nebenwirkung eines Arzneimittels nachgewiesen ist. Schon wenn auf Grund eines ernst zu nehmenden Verdachts zu befürchten ist, dass ein Medikament zu Gesundheitsschäden führt, sieht sich der Verbraucher vor die Entscheidung gestellt, ob er eine Verletzung seiner körperlichen Unversehrtheit riskieren will oder nicht". LG Aachen, 18. 12. 1970, JZ 515.

<sup>263</sup> LG Aachen, 18. 12. 1970, JZ 515.

<sup>264</sup> LG Aachen, 18. 12. 1970, JZ 517.

<sup>265</sup> BGH 11. 7. 1972, VersR 1972, 1075 (1078).

does not point to the specificity of the risk, and can be taken as for granted, given that this danger affects also other treatments. It is precisely because this same risk is more severe and more probable in the injection of Estil, that it must be prevented through special instructions.<sup>266</sup>

To the objection that the pharmaceutical firm can only be responsible for damage caused by an adequate use, the sentence contests that this is valid for conscious errors, but do not release the company from warning against a predictable misuse (“naheliegender Mißbrauch”). This is precisely the case, where additional communication precaution can prevent damage.<sup>267</sup> Responsibility for product *use* falls on the doctor, but not exclusively on him: the complexity of the pharmaceutical offer and the insufficient knowledge about product development and features demand higher information and warning requirements from the side of those, who are responsible for the *product*.<sup>268</sup>

More importantly, the sentence establishes that the instruction and warning requirements related to pharmaceuticals are higher than those concerning other products.<sup>269</sup>

The Estil sentence concerns instructions accompanying the product and formulates specific requirements for pharmaceuticals: product information must be determined by the purpose of preventing any predictable damage. The company must not merely inform about possible risks, but also indicate how the product is to be safely assumed, together with countermeasures and actions, which shall be undertaken in case of adverse reactions. Specific warnings should also caution about the severity of the consequences of not following the instructions.

Another important sentence for the determination of instruction duties is BGH 24. 1. 1989 – the asthma spray case.<sup>270</sup> It parallels the Estil sentence in emphasizing the importance of specific warnings against misuse, especially for drugs which are intended to be used in dramatic situations, such as an asthma attack.

By coming after the separation of patient instructions from specialist information for the doctor (AMG 1986), this is the first sentence which specifically addresses the package leaflet as a source of information for the lay user.

The sentence refers to a case of death followed to the overdosage of an asthma spray in the course of a severe asthma attack. The pharmaceutical firm is charged of insufficient warning about the consequences of misuse. The information provided in the package leaflet in fact is complete but does not explain with sufficient emphasis the entity of health damage which the spray can produce in excessive dosage.<sup>271</sup> The

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<sup>266</sup> BGH 11. 7. 1972, VersR 1972, 1076.

<sup>267</sup> BGH 11. 7. 1972, VersR 1972, 1077.

<sup>268</sup> BGH 11. 7. 1972, VersR 1972, 1076.

<sup>269</sup> “An die Aufklärung über mögliche Gefahren, die von Arzneimitteln ausgehen, sind besonders strenge Anforderungen zu stellen”. BGH 11. 7. 1972, VersR 1972, 1076.

<sup>270</sup> BGH 24. 1. 1989 (VI ZR 112/88, Frankfurt am Main) VersR, 1989: 399 (401).

<sup>271</sup> The sentence acts report the incriminated passages: “Dosierung. Bei drohendem oder akutem Asthmaanfall genügt meistens ein Aerosolstoß, um eine sofortige Atmungserleichterung zu erzielen. Hat sich die Atmung nach fünf Minuten nicht spürbar gebessert, kann ein zweiter Aerosolstoß genommen werden. Wenn bei einem besonders schweren Asthmaanfall nach weiteren fünf Minuten noch keine

court underlies that in general no duty of warning against overdosage is part of the instructions which the pharmaceutical producer owes to the product consumer, however it argues that specific warnings of this type must accompany pharmaceuticals, when they are intended to be used in dramatic situations directly by the patient.<sup>272</sup>

The importance of the Asthma-spray sentence lies in its emphasis on product instruction as a privileged means of risk prevention for the lay consumer. Completeness of information is not sufficient; information must also actively foresee and address possible areas of misuse and abuse, to which the consumer might be reasonably induced in his particular case.

The Estil and the Asthma-spray sentences are both concentrated on safety aspects of pharmaceutical information (risk prevention), whereas the Contergan sentence also refers to product information in the context of risk disclosure for self-determination (autonomous decision about unavoidable risk).

## 2.2 Product instruction in the AMG

The considerations developed in the Contergan and Estil sentences have been partly included into the paragraphs devoted by the AMG to product instruction. However, in the AMG, obligations related to safety concerns (“Verkehrspflicht”) more than the autonomy aspect of information are on focus.

No explicit mention is devoted to the qualification of risk information as a condition for the respect of lay consumers’ autonomy. This is partly due to historical reasons: in fact, only since 1986 did regulation introduce pharmaceutical information specific for the drug user.

In fact, the official motivation for the introduction of product information is that it should guarantee a safe and correct use of the product by means of appropriate instructions with no distinction between the doctor and the end-user.<sup>273</sup>

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befriedigende Atmungserleichterung erzielt wurde, kann eine dritte und für diesen Anfall letzte Inhalation vorgenommen werden. Die nächste Inhalation (ein bis drei Atemzüge) soll dann frühestens nach zwei Stunden vorgenommen werden. ... Nebenwirkungen und Begleiterscheinungen: ... Bei besonderer Empfindlichkeit und/oder höherer Dosierung können feines Fingerzittern, Unruhegefühl oder Herzklopfen auftreten. Auch Schwindel, Kopfdruck oder Schwitzen sind vereinzelt beobachtet worden. Beim Vorkommen dieser Erscheinungen soll die Dosis verringert werden ... Besondere Hinweise: Bringt die Behandlung in der empfohlenen Dosierung nicht den gewünschten Erfolg, so spricht der Krankheitszustand auf die Behandlung ungenügend an, weil andere Krankheitsursachen daran beteiligt sind. Es ist daher unverzüglich ärztliche Beratung erforderlich, damit der Behandlungsplan neu festgestellt wird“ BGH 24. 1. 1989 (VI ZR 112/88, Frankfurt am Main) VersR, 1989: 399.

<sup>272</sup> „Der Revisionserwiderung ist zwar darin zu folgen, dass bei Arzneimitteln grundsätzlich nicht vor den bei einem exzessiven Gebrauch eintretenden Gefahren zu warnen ist bzw. vor einer missbräuchlichen Verwendung, die als unvernünftig gelten muss. Bei Arzneimitteln jedoch, die dazu bestimmt sind, dass sie – wie etwa ein Dosier-Aerosol in Asthmaanfällen – von dem Patienten selbst in dramatischen Situationen angewendet werden, sind auch Warnungen vor den bei exzessivem Gebrauch auftretenden Gefahren erforderlich“. BGH 24. 1. 1989 (VI ZR 112/88, Frankfurt am Main) VersR, 1989: 401.

<sup>273</sup> See amtliche Begründung zu § 11 AMG, printed in Kloesel A., W. Cyran, Arzneimittelrecht mit amtlichen Begründungen, weiteren Materialien und einschlägigen Rechtsvorschriften sowie einer

In general, it can be said, that the law emphasizes the role of risk communication as a risk prevention tool and as an instrument of scientific information about the chemical molecule.

However, the acknowledgment of unavoidable risk (“Nebeneffekte” § 4 AMG) and the association of liability sanctions for failures to instruct about them, implicitly qualifies this information as information for decision autonomy.

Product information liability is regulated through the second paragraph of § 84 I AMG, which link the conditions for compensation to instruction failure: “the damage could have been foreseen by the producer, and has not been communicated in the medical information or in the patient package leaflet”.<sup>274</sup>

§ 10, 11 AMG are norms of circulation duties (“Verkehrspflicht”) and prescribe strict requirements as to labeling and product instruction that should be included in the package.

According to § 11, which prescribes sequence and form of the contents, the PL must contain following sections: indication, contraindications, precautions, therapy dosage and duration, interferences with other drugs or specific foods, adverse drug reactions, expiry date, last date of information update.

A fundamental evolution in the regulation of product information has been reached through the separation of lay from expert information. This dates back to 1986, with the II amendment to the law (16.8.1986 – BGBl. I S. 1296): the purpose of this amendment was precisely to facilitate comprehension for the end-user. Product information comprises than, the so called “Summary of Product Characteristics (SPC)” and the Patient Package Leaflet (PL); the first directed at the health professional, the second at the patient.

By disentangling patient information from information directed at the doctor, the legislator explicitly turns the end-user to be the addressee of PL information.

Through this intervention product information becomes a specific information vehicle from pharmaceutical company to the end-user which is autonomous from the instructions provided by the doctor during the consultation, and whose purpose is not limited to safe use promotion, but, in the case of unavoidable (residual) risk, for which no adequate countermeasure can be taken in order to prevent it, also extends to the provision of information for an autonomous decision.

In fact, because of the specific nature of pharmaceuticals as ‘unavoidably unsafe products’ not all risks can be prevented through adequate precautions. An absolute risk-free guarantee can only be the overall renounce to the therapy. Thus, the reason for informing the user about unavoidable side-effects cannot be that of averting them through adequate countermeasures, but rather to enable him *decide* whether to take the risk or not. Analogously to the distinction of risk and safety information in the doctor liability law, also in the case of product instruction for pharmaceuticals it can be distinguished between precautionary warnings and risk disclosure.

In liability litigations a faulty product instruction can constitute a count of indictment in two ways:

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Sammlung gerichtlicher Entscheidungen, Kommentar, Stuttgart, 1973, cited a. o. in Krudop-Scholz, 2005: 137, footnote 740.

<sup>274</sup> § 84 I 2 AMG.

- from a safety perspective, the warning could have been not sufficient or not sufficiently emphasized as to promote adequate use and correct behavior in the user.
- from an autonomy perspective, the information about the occurred damage would have led the user to a different therapeutic decision – for instance to renounce to the drug – and therefore would have prevented the damage.

Anyhow, because product instruction faultiness falls under tort liability, compensation is granted independently of the damage tolerability. The liability table is presented again below, with special focus on tort liability for instruction faults:

		<i>Appropriate product instruction</i>	<i>Faulty instruction</i>
<b><i>Intolerable damage</i></b>		Strict liability: Compensation according to § 84 I Abs. 1 Nr. 1 AMG	Tort liability: compensation according to § 823 Abs. 1 BGB or § 84 I Abs. 1 Nr. 2 AMG
<b><i>Tolerable damage</i></b>	<b>Not irrelevant</b>	<b>No compensation</b>	Tort liability: <b>compensation</b> according to § 823 Abs. 1 BGB or § 84 I Abs. 1 Nr. 2 AMG
	Irrelevant	No compensation	No compensation

**Tab. 1: Concurring factors in liability distribution as regulated by § 84 AMG (strict liability and instruction failure) and civil tort liability § 823.1 BGB: Violation of instruction duties and damage entity.**

The direct consequence of the respect for decision autonomy through risk disclosure is a discharge from responsibility about disclosed risks,<sup>275</sup> in that pharmaceutical product instruction about unavoidable risks translates in a reallocation of risk responsibility from producer to user.

This parallels the institution of informed consent in medical communication. The double character of consent consists namely in two parallel functions:<sup>276</sup>

- *removal of illegitimacy of bodily offence*: through consent the bodily invasion ceases to be illegitimate in that it is allowed by the owner of the body's jurisdiction;
- *liability disclaimer for disclosed risks*: for unavoidable risks related to the intervention, which have been disclosed, the doctor assumes no responsibility.

The drug information provided to the patient in the PL is a form of risk information and of expert-to-lay communication which parallels the functions attributed to doctor's communication. Patient's responsibility in the therapeutic decision has been also indirectly emphasized by the separation of specialist (SPC) from lay (PL) information.

In this setting, the pharmaceutical firm is liable for the product and the up-to-datedness of the related information (to both doctor and end-user); the doctor is responsible for adequate prescription and risk information; finally, the patient is supposed to shoulder the residual risk coming from the therapy if adequately informed by the doctor *and* by the pharmaceutical firm through PL.

<sup>275</sup> Zacharias, 1986:356 f., speaks of a „Freizeichnung“: exclusion of liability. Similarly Schlund, 1999: 771. See also chapter 4 for discussion.

<sup>276</sup> See Koyuncu, 2005b: 290. See next two chapters for detailed discussion.

However, in the case of PL information, doubts have been raised as to the real contribution brought about by this information means in providing the end-user with suitable tools for an autonomous decision.<sup>277</sup>

Moreover, consent to therapy is given to the doctor during consultation and therefore PL information is acquired when a decision has apparently already been made. The function of product information needs thus to be investigated in the wider framework of therapeutic pharmaceutical communication.

### **3. Summary and conclusion**

This chapter has provided an outline of the liability regimes for pharmaceutical products. These distinguish among each other for the requirement of breach of law, tortiousness, and damage tolerability.

No damage is required for a pharmaceutical firm to incur in criminal liability, but simply a breach of law. Entity and conditions of sanctions are regulated by § 95 AMG.

As for civil liability, which regulates litigations between drug consumer and producer, relevant liability regimes are tort and strict liability.

Tort liability (§ 823.1 and 2 BGB) presupposes that the damage has been caused by the violation of a professional duty. Compensation is not linked to the tolerance threshold: relevant damages are compensated even if they do not trespass the tolerance threshold established by the law.

Strict liability instead has been introduced in order to cover those cases, where no duty infringement can be ascribed to the producing firm, but nevertheless the importance of the damage requires an economical compensation as minimal reparation of the damage suffered by the drug user.

The practical relevance is however of reduced importance given that it covers only damage which fall beyond the tolerance threshold established by the law. In fact the residual risk threshold established by the risk/benefit evaluation in the approval phase must take into account not only safety concerns but also questions of health care provision, and therefore tends to be set high enough as to allow for the medical care of the largest possible risk group. This may however result in specific cases of damage which exceed the benefit expected by the individual user. Although these types of damage are not irrelevant and indeed sometimes are of considerable entity, they are not covered by strict liability because they do not exceed the general tolerability threshold.

Liability for product instruction failures falls under tort liability and is regulated by § 823.1 and 2 BGB and § 84 I 2 AMG.

PL information belongs both to product liability and safety regulation requirements, and responds both to risk prevention purposes and to the legislator's concern of warranting decision autonomy. Within this second function however, risk communication results also in a reallocation of responsibilities about eventual damage in the realm of residual risk.

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<sup>277</sup> See a. o. Henning, 1996: 342 f.

As a further contribution to the analysis of the institutional setting in which the PL is embedded, doctor's information duties are examined in the next chapter, with a special attention to professional obligations related to pharmaceutical prescription.

# 3 Informed Consent

*“Vertrauen ist akzeptierte Abhängigkeit”  
(Trust is acknowledged dependency)  
Dinnendahl, 1981.*

## 1. Introduction

This chapter analyzes the institute of informed consent and investigates its implications as for the amount, type and detail of information received by the drug consumer.

Basing on the standard typology which distinguishes among informed consent, and shared decision making (entailing a counseling activity from the side of the doctor), the actual liability setting will be scrutinized as a steering factor in the consolidation of one type of therapeutic decision-making rather than the other.

This analysis will constitute the basis for examining the legal status of PL information within the institute of informed consent and for evaluating PL information within this institute.

## 2. Pharmaceutical communication to the patient: Patient Package Leaflets and doctor’s information

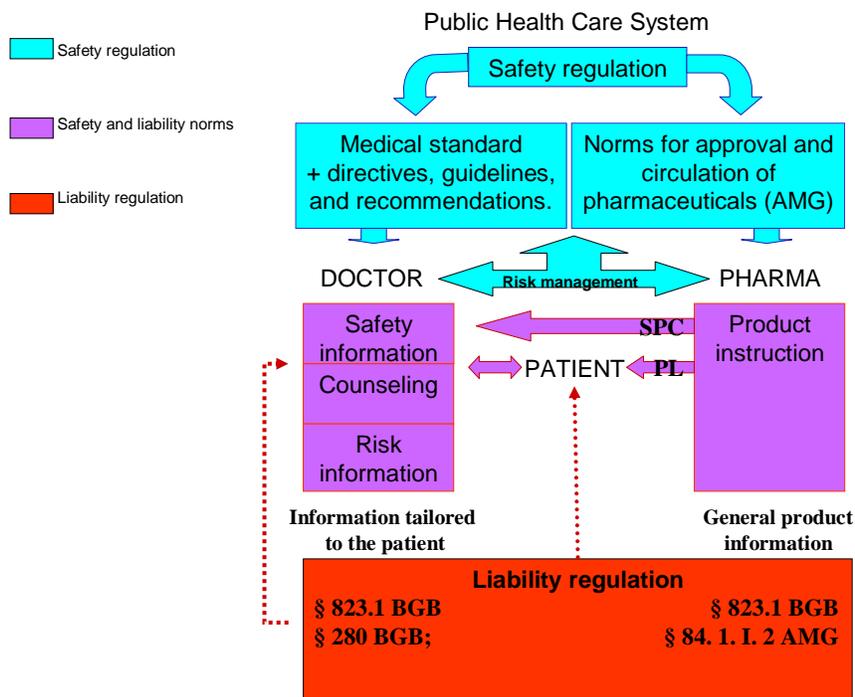
In the first two chapters I have illustrated the safety and liability regulation related to pharmaceuticals. The two systems both aim to reduce risk to the minimum through a set of preventive (approval, risk management) and deterrent (damage liability) norms.

The safety system as illustrated in the first chapter is concerned with the product safety evaluation at time of approval – and afterwards – through a system of risk prevention. It directly concerns however only the pharmaceutical firm as a norm addressee. An equivalent risk prevention system for the doctor’s professional performance is limited to the issue of medical directives, guidelines, and recommendations.

Liability regulation is also asymmetric: whereas the doctor must respond both for contractual duties (§280 BGB) and for tortuous acts (§823.1 BGB); the pharmaceutical firm is not liable for contract violations towards the patient, but only for torts (§823.1 BGB; §84.1.I.2 AMG).

Risk information delivered to the patient reflects this complex arrangement in that its contents and configuration are stipulated by safety norms; but are also indirectly shaped by the stakeholders' interest in avoiding liability charges.

In figure 1 the drug end-user (patient) is represented at the center of this communication flux: The doctor is considered to be the main responsible for adequate drug selection, prescription and information: in this setting the PL represents a special support for expert-to-lay communication.



**Figure 5 Pharmaceutical information to the patient: safety and liability norms impinging on the communication system.**

Tailored information is principally delivered through the doctor, who must respond for his therapeutic choice and related information. The pharmaceutical firm provides both users (doctor and patient) with general product information: Summary of Product Characteristics for the doctor and PL for the patient: sequence and contents of the information are strictly regulated through §§ 11 and 11a AMG respectively. Therefore, the principle responsible for PL configuration and content is the legislator that prescribes through these norms the adherence to a standardized information design and layout.

The purposes underlying both PL and doctor information are determined by patients' right to bodily integrity and autonomous choice. However, the norms aiming at

protecting autonomous choice have been until recently subordinated to bodily injury in that the institute of informed consent which is supposed to warrant the patient's right to self-determination has been traditionally regulated within tort liability (§ 823.1 BGB), which in the German setting does not comprise violation of immaterial rights (such as freedom of choice). This setting has consolidated a specific model of informed consent which lends itself to fundamental critics.

The recent amendment of the compensation law,<sup>278</sup> which allows claims for immaterial damage following from contractual violations, assigns an autonomous value to the freedom of choice, independently from bodily injury, and thereby extends the doctor's information duty to a counseling activity which aims at enabling the patient's choice, rather than simply obtaining a valid consent through risk disclosure. This chapter investigates the communication model implicated by the theory of informed consent (tort liability) and compares it to the template outlined by the shared decision making model. The aim is to provide a basis for the evaluation of the legal status of PL information within the therapeutic decision (chapter 4).

### 3. Medical standards and required level of care

The regulation of the medical profession is not comprised in a single specific law, but has rather consolidated through a long series of court decisions on the basis of civil norms such as § 280 BGB (compensation for violation of contractual duty) and § 823 (1) BGB (compensation for damage caused by unlawful acts).<sup>279</sup> In both norms the distinction between residual risk and medical error (negligence) is essential in order to ascribe responsibility to one or the other party. Only damage originated by medical error falls upon doctor's liability. Residual risk instead must be shouldered by the patient, *unless it has not been adequately communicated prior to the intervention/therapy*. It is therefore comprehensible that much attention is devoted to the criteria establishing the threshold line between medical error and residual risk on one side, and to the determination of the amount and level of detail of the information about residual risk on the other.

The point of reference for establishing when the medical procedure, which led to health damage is to be considered as negligence (Behandlungsfehler) is the medical standard.<sup>280</sup> The doctor is not supposed to guarantee therapeutic success, which is unfortunately not entirely under his control. But he is requested to perform his task with careful endeavor to heal, and according to professional standards of quality.<sup>281</sup>

According to a prevalent definition, "the medical standard represents the standard of medical sciences and medical practice, that are necessary to the achievement of the therapeutic purpose, and that have been proofed through experience"<sup>282</sup>.

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<sup>278</sup> II Schadensersatzänderungsgesetz, 2SchadÄndG: 25.7.2002 BGBI I S 2674.

<sup>279</sup> Krudop-Scholz, 2005: 63. See also chapter 2 for details about § 823 BGB.

<sup>280</sup> Krudop-Scholz, 2005: 67.

<sup>281</sup> Krudop-Scholz, 2005: 115.

<sup>282</sup> "Standard in der Medizin repräsentiert den jeweiligen Stand der medizin-wissenschaftlichen Erkenntnisse und der ärztlichen Erfahrung, der zur Erreichung des ärztlichen Behandlungsziels erforderlich ist und sich in der Erprobung belegbar bewährt hat". Scheu, 2003: 711, drawing with unessential variations on the

The medical standard consists therefore of three principal elements, which jointly contribute to the articulation of its meaning:

- scientific knowledge<sup>283</sup>;
- medical practice;
- professional acceptance.<sup>284</sup>

A practical consequence of this articulation is the interdependence and reciprocal balancing of these dimensions when one or more of them do not prove to be at the optimal level: for instance, the fewer the scientific proofs at hand, the stricter must be the requirements of professional acceptance; the higher the professional acceptance, the lower can be the quantity of personal experience with the therapy (medical practice).<sup>285</sup>

In order to institutionally establish and implement the medical standard, three kinds of norms are distinguished according to their binding character: directives, guidelines, and recommendations.

Directives are strictly binding, and non-compliance to their rules leads to sanctions.

Guidelines instead, represent medical decision supports that are systematically developed in order to assist practitioners in the adequate procedure for specific health problems. Deviation from the proposed measures is allowed (and sometimes required) in specific cases. The degree of binding force depends on the level of scientific evidence substantiating the guideline: the greater the scientific and/or epidemiologic support, the stronger are the conditions required for deviating from them.

Recommendations are the description of one possible procedure with no binding force: their value is limited to counseling.<sup>286</sup>

Directives, guidelines, and recommendations constitute a reference for the doctor in determining if he is acting with compliance to the required level of care. However, it is the doctor's task to discern in each single case to what extent he is bound to the established norms, or if the specific situation require a deviation from it.

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definition of Carstensen: Carstensen, G. „Vom Heilversuch“ in DÄBI, 1989, B-1737, cited in Hart, 1998b: 170.

<sup>283</sup> Applied medicine is increasingly influenced by the principles of Evidence Based Medicine. EBM aims at the standardization of epidemiological data and improvement of medical decisions through the issue of guidelines supported by coordinated statistical data.

Scientific methodology in this field is deeply influenced by the epidemiological approach with related ranking of evidence value as a function of the way data are collected:

1. double-blind, randomized clinical studies;
2. controlled clinical studies;
3. epidemiological studies;
4. case studies;
5. therapy observations. Francke, Hart, 1999: 26.

The medical profession in general and some exponents in particular express their reserves as to the exclusive prerogative given to this method to the detriment of the traditional qualitative approach: Ewig, 2006: 73-74.

<sup>284</sup> Francke, Hart, 1999: 22.

<sup>285</sup> Francke, Hart, 1999: 24, 26.

<sup>286</sup> Francke, Hart, 1999: 23-25.

Professional care duty refers to, but must also go beyond standardized rules whenever the circumstances demand it.<sup>287</sup>

Medical error as a result of non-compliance to professional standards represents a breach of contractual duty in the sense of § 276 I 1 BGB, which activates compensation rights in case of damage for the counterpart (§ 280 BGB).<sup>288</sup>

If therapy failure or worsening cannot be ascribed to medical error, than it cannot be imputed to the doctor's performance, and is considered *residual risk*. The task of judicature in this field consists precisely in the case to case distinction between medical error and residual risk.<sup>289</sup>

#### 4. Doctor's professional duties

The medical professional duty comprises following tasks:<sup>290</sup>

1) *Diagnosis.*

The standard of care translates in the gathering of relevant information for a sufficiently confident diagnosis: the data comprise patient anamnesis and observation, eventual labor tests, and diagnostic interventions. Not only the amount of diagnostic measures but also the interpretation of the data deriving from them must adhere to the professional standard so that the personal judgment of the doctor cannot unjustifiably deviate from it.<sup>291</sup>

2) *Therapeutic decision.*

This is principally the doctor's task<sup>292</sup>: if the patient refuses or does not comply to the therapy, he acts at his own risk. This is a logical consequence of the fact, that the patient consults the doctor, precisely as a reference for an expert and informed decision. The importance of this perspective is decisive when considering information duties.<sup>293</sup>

3) *Intervention/therapy.*

This is the core duty of medical care: both for surgical interventions as well as for conservative therapies the compliance to medical standards constitute the fundament of professional performance and its legitimation.

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<sup>287</sup> Francke, Hart, 1999: 26-27.

<sup>288</sup> § 276 BGB refers to an objective level of care specific for the profession (due diligence): Krudop-Scholz, 2005: 115. The extent of the required level of care also depends from the value of the concerned good, from the dimension, probability and reversibility of danger, and from illness severity. The upper limits are determined by feasibility considerations and economic factors: Wagner, 2004: 1827, Rdnr 676, 1832 Rdnr 688.

<sup>289</sup> Wagner, 2004: 1834, Rn. 692, citing BGH, NJW 1985, 2193 f.

<sup>290</sup> See Wagner, 2004: 1832 ff. See also Francke, Hart, 1999: 34 ff. for a detailed account of doctor's duties within and beyond the therapeutic task (keep informed, filing of therapy documents, etc.).

<sup>291</sup> Francke, Hart, 1999: 34 ff.

<sup>292</sup> Wagner, 2004: 1833, Rn. 689; see also Francke, Hart 1999: 122.

<sup>293</sup> Wagner, 2004: 1833, Rn. 689.

#### 4) *Post-therapeutic care.*

Observation of the post-therapeutic course and related counseling duty.

All these tasks must be performed in compliance with professional standards of care.

### **4.1 Information duties: the protection of safety and decision autonomy**

Communication is a paramount factor along the entire course of the medical therapy. The information due to the patient is divided into two broad categories: “Sicherungsaufklärung” (safety information) and “Selbstbestimmungsaufklärung” (information for self-determination).<sup>294</sup>

Safety information should avoid foreseeable damage by instructing about adequate therapeutic behavior; information for self-determination aims to make the patient knowledgeable of the residual risk connected to the therapy, and which must be taken into account because it is not ascribable to medical error.

#### **i. 4.1.1 Safety information**

Safety information consists of warning for the safe use of the drug or for a cautious behavior during and after the treatment or surgery. It is aimed at preventing avoidable damage by instructing the patient about the correct therapeutic behavior.<sup>295</sup> In the post-therapy phase, this can translate in the information about the necessary measures for preventing complications and eventually insistence in the danger represented by non-compliance.<sup>296</sup>

Because patient’s compliance is essential to therapy success and safety, it is part of the doctor’s information duty not only to provide warnings and instructions, but also to create the premises for a cooperative and trustful relationship with the patient.<sup>297</sup> He must secure compliance also by informing about the risks deriving from non-adherence to his instructions, and in general must secure that the patient is aware of all necessary diagnostic and precautions measures which the patient should follow during and after the therapy.<sup>298</sup>

#### **4.1.2 Information for self-determination**

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<sup>294</sup> See also Francke, Hart, 1999: 55 ff.

<sup>295</sup> BGH 22.1.1960 (VersR 60, 417-19). See also Krudop-Scholz, 2005: 70.

<sup>296</sup> Francke, Hart, 1999: 49.

<sup>297</sup> Krudop-Scholz, 2005: 71-73. The term “compliance” has been accused of paternalistic connotations. Substitutes such as “accordance”, “concordance”, or “alliance” have been proposed by different scholars: this does not change much to the substance of the discussion, given that, even if the therapeutic choice is the result of a shared decision, nevertheless, after a decision has been made, it is the doctor who must give therapeutic instructions, and the patient who must follow them.

<sup>298</sup> BGH 22.1.1960, VersR 60, 418: „[Der Arzt] muss alles in seinen Kräften Stehende tun, um ihn vor Schaden zu bewahren“; BGH 7.7.1994, NJW 94, 3012. See also Francke, Hart, 1999: 178-179.

Information for self-determination should warrant the patient's freedom of choice and right to self-determination. Because of the risk associated to the medical intervention/therapy, this freedom of choice especially relates to the residual risk, whose responsibility is not ascribed to medical error and must be therefore shouldered by the patient.

Residual risk represents the risk that accompanies the beneficial offered by the intervention, and that the patient can decide to undertake if he does not want to give free course to his disease in the light of personal considerations and preferences. The right to self-determination prescribes that the patient is aware about it in order to make an informed decision.

Information for self-determination should help the patient make his decision by providing him with essential data about therapy importance and risk implications.<sup>299</sup>

It is further specified in subcategories such as diagnosis disclosure, risk-information, information about the emergency of the intervention, probability of success.<sup>300</sup>

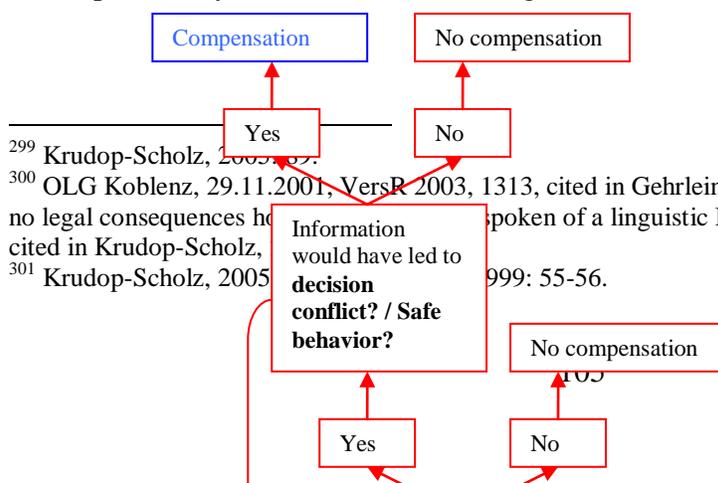
The doctor is not supposed to give all possible medical details, but on the contrary, he must select information, which he deems relevant for the personal situation of the patient.<sup>301</sup>

#### 4.2 Compensation of material damage for violation of information duty

Compensation for material damage claimed on the basis of violation of information duties is fundamentally decided along three conditions:

1. Was there a duty to inform on the basis of the medical knowledge available? (duty to inform)
2. Was the information delivered in sufficient and adequate way? (breach of duty)
3. Was the failing of providing due information relevant for damage occurrence? (causality of breach for damage): Depending on the nature of information, causality for damage can be established in two different senses:
  - a. In the case of safety information, a warning failure can be *at the origin of the damage in the sense that the patient would have not been damaged if, adequately informed, he would have behaved consequently.*
  - b. In the case of information for self-determination, the causality link depends on the *materiality of the information to the decision*: Was the missing risk information relevant to the decision? Or would the patient have decided in the same way, also if adequately informed about the damage for which he is suing the doctor?

The following scheme summarizes the liability framework which regulates doctor responsibility in case of health damage:



<sup>299</sup> Krudop-Scholz, 2005, 27.

<sup>300</sup> OLG Koblenz, 29.11.2001, VersR 2003, 1313, cited in Gehrlein, 2004: 1495. This subclassification has no legal consequences but is spoken of a linguistic Babylon (Deutsch, VersR, 1981, 293,

<sup>301</sup> Krudop-Scholz, 2005, 27, 999: 55-56.

**Figure 6: Algorithmic scheme for liability compensation in case of health damage**

Compensation takes place only if it can be established, that along the medical knowledge available at time of therapeutic consultation, there was a duty to inform about the risk of a damage, as the one under consideration in the litigation; that the doctor has failed to (adequately) inform about it; and that the patient would have behaved differently/ would have found himself in a decisional conflict, if informed about it.

A legal consequence of this setting is that the patient shoulders the risks, he has been made aware of prior to intervention/therapy.

### **4.3 Compensation for moral damage: violation of the freedom of choice**

Until the 2<sup>nd</sup> Amendment Law of Compensation (2002),<sup>302</sup> cases of liability litigations sued on the basis of information duty violations were exclusively linked to material damage.<sup>303</sup> In fact, compensation for moral damage (damage for pain and sufferings) was limited by § 847 BGB to torts, and could not be claimed for breaches of contract.<sup>304</sup>

Through the 2<sup>nd</sup> Amendment Law of Compensation the norms related to compensation for tort and contract liability have been harmonized,<sup>305</sup> so that compensation for the failure to provide information for self-determination needs not be necessary linked to damage: therapeutic information disentangles from the theory of informed consent and aspires to provide the patient a basis for autonomous choice beyond the disclosure of residual risk.

### **5. Legal foundations of the duty to provide information for self determination: tort liability and contract obligations**

Information about the unavoidable risks related to the intervention is due to the patient under the general framework of constitutional norms concerning respect for autonomy and the connected protection of constitutional goods such as the right to self-determination and human dignity.<sup>306</sup> This is the concretization in civil law of the general freedom rights protected by the constitution through § 2 I GG.<sup>307</sup>

The right to self-determination though breaks down in the medical choice into two distinct rights.<sup>308</sup>

- a. The right to allow the doctor invade one's bodily integrity (jurisdiction over one's own body);
- b. The right to choose the therapy and being enabled to do so.

The role of information in tort liability refers to the first right: within this charge, information provided by the doctor prior to intervention acts as a legitimization of the

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<sup>302</sup> II Schadensersatzänderungsgesetz, 2SchadÄndG: 25.7.2002 BGBl I S 2674.

<sup>303</sup> Although liable for both breach of contract and bodily injury (see RG 14.3.1911, JW 1911: 450), traditionally, the doctor has generally been prosecuted on the basis of a tort charge (§ 823.1 BGB), rather than of a breach of contract (§§ 278, 280 BGB) – whether or not the claim was medical error or violation of information duty. This is fundamentally due to procedural reasons: the different legal position of the prosecutor as for prescription times (Verjährungszeit) and damages for pain and suffering (Schmerzensgeld). Kern, Laufs 1983: 155, cited in Glatz, 1998: 233. This setting is actually being modified by the II Schadensersatzänderungsgesetz, 2SchadÄndG.

<sup>304</sup> Wagner, 2004: 1810, Rn.643.

<sup>305</sup> This harmonization is related to the amendment of § 253 Abs. 2 BGB and the abolishment of § 847 BGB

<sup>306</sup> See also Wagner, 2004: 1494 for a discussion about the binding force of the constitution in relation to civil law.

<sup>307</sup> Krudop-Scholz, 2005: 85-86.

<sup>308</sup> See Hart, 1998c: 302 ff. for legally detailed discussion.

doctor's invasion of bodily integrity, and results in a disclaimer of the resulting residual risk. Here the right to self-determination is called into question only indirectly as a guarantee that through information, the patient has *validly* consented to the intervention.

The second right is accounted for through the professional duty to inform as it is implicated by the expert-to-lay relationship within contract obligations: in this context information disclosure is a professional duty owed to the patient, in order to *enable him to make an informed decision*. Here the right to self-determination is treated as a right on its own.

The two forms of information duty result in a different communicative status of risk information, and in a different structure of the doctor-patient communication.

Within the theory of informed consent, the point of providing the patient with information for self-determination is the adequate information about the nature of the intervention and the related residual risk, so that the patient can knowingly undergo the unavoidable risks related to the therapy and the medical invasion of bodily integrity is deprived of its illegitimacy through the patient's informed *consent*.

Instead, the contractual duty to inform the patient about the residual risks related to the therapy is part of a broader counseling duty which should enable the patient make an informed *choice*.<sup>309</sup> The distinction is all but secondary and leads to different communication structures. Fundamentally, the informed consent model is blamed to reduce the doctor-patient communication to a risk disclaimer,<sup>310</sup> whereas the contractual model of doctor-patient communication rather approaches a counseling model of expert-to-lay communication.

## **5.1 Tort liability and right to self-determination as jurisdiction over one's own body**

Tort liability for violation of information disclosure is based on the doctrine of bodily offence ("Körperverletzungsdoktrin"). According to this theory, which goes back to the first pronouncements on medical liability, the medical intervention is illegitimate on principle (tort against bodily integrity and health), unless justified by the willful consent of the patient.<sup>311</sup> This is valid independently from purpose, outcome and compliance to standard levels of medical care.

Because freedom rights protect the autonomy of the single individual, violations of these freedoms, when occurring *with consent* of the concerned person, cease to be such.<sup>312</sup>

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<sup>309</sup> Damm, 2006: 5, 12, with reference to Hart, 2003 MedGen: 60, 62.

<sup>310</sup> Damm, 2006: 2; Hart, 1998c: 310

<sup>311</sup> RG 31.5.1894, Strafs. Bd. 25 nr. 127: 375. Francke, Hart, 1999: 114-115, 117.

<sup>312</sup> See Murswieck, Dietrich, 'Art. 2. Freie Entfaltung der Persönlichkeit, Recht auf Leben, körperliche Unversehrtheit, Freiheit der Person.', in Sachs, 1999: 161, Rn. 15.

BGH 16.12.1953 (VersR 1954, 98); Martin, 1954: 329-330; BGH 10.7.1954 (NJW 1956, 1106 = VersR 1954, 496); BGH 28.11.1957 (NJW 58, 267-69); BGH 9.12.1958 (NJW 59, 811-14); BGH 9.12.1958 (NJW 1959, 814-15 = VersR 1959, 153-55).

However, in this setting the reference to freedom rights is only functional to the justification of the violation of bodily integrity. Tort litigations, are in fact subsumed under § 823.1 BGB<sup>313</sup>, according to which the defendant must respond for *health* damage occurrence. The independent violation of the right to self-determination is not contemplated by tort liability law: § 823.1 BGB covers only fundamental goods, such as life, health, body, (physical) freedom, ownership; but not the right to know, to choose and to self-determination. Even if the good protected by risk information duty is self-determination, when no health damage occurs, no compensation is granted even if there has been no adequate information.

From a formal point of view, this setting results in the subordination of the protection of the right to self-determination to the violation of bodily integrity.<sup>314</sup> Only when a health injury has occurred, is the right to self-determination called into question.

In fact, the duty to inform grounds on the right to self-determination only indirectly, because its offence invalidates the consent, but violation of this duty does not *per se* constitute a charge.<sup>315</sup> The legal construction of the information duty requirement can be represented as follows:

1. A medical intervention is fundamentally an invasion of bodily integrity and health (Körper- und Gesundheitsverletzung; protected by Art. 2 II GG)<sup>316</sup>;
2. The illegitimacy of this action is removed by the patient consent (*“volenti non fit iniuria”*);
3. *The consent is valid only if it respects the patient’s right to self-determination;*
4. For this to be respected, the patient must be adequately informed.

The offence of the right to self-determination is related to the medical intervention only *through* the consent condition and the causality requirement that the due additional information would have put the patient into a decision conflict which would possibly lead him to give no consent to the procedure.<sup>317</sup>

A series of incongruities related to this framework have been identified by legal literature and health professionals alike.<sup>318</sup> If some legal theorists lament that *this*

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<sup>313</sup> Bürgerliches Gesetzbuch (Civil Code): Deliktstatbestand: unerlaubte Handlung (Offence: Tort). The subsumption of medical intervention under the offence of “Körperverletzung” (violation of bodily integrity) date back to the XIX century: RG 31.5.1894 (Strafs.Bd. 25 nr. 127, 375). In the following years court decisions reject the exceptionality of the medical intervention in this sense: RG 27.5.1908 (RGZ 68, 431[438]). Subsequently all courts have based their decisions about damages compensation on this tort: RG 19.6.1936 (RGZ 151, 349[352]); RG 7.10.1937 (JW 1937, 3087-92); RG 8.3.1940 (RGZ 163, 129[139]); RG 3.12.1941 (RGZ 168, 206 [214]).

<sup>314</sup> This argument is among others at the basis of the amendments proposed by Hart, 1998c: 311.

<sup>315</sup> § 2 I GG (Grundgesetzbuch: Constitution) protects the right to personality and grounds the right to self-determination: “Jeder hat das Recht auf die freie Entfaltung seiner Persönlichkeit, soweit er nicht die Rechte anderer verletzt und nicht gegen die verfassungsmäßige Ordnung oder das Sittengesetz verstößt“. § 2 II GG protects bodily integrity and freedom in a physical sense: “Jeder hat das Recht auf Leben und körperliche Unversehrtheit. Die Freiheit der Person ist unverletzlich. In diese Rechte darf nur auf Grund eines Gesetzes eingegriffen werden”.

<sup>316</sup> BGH 9.12.1958, NJW, 1959, 811 ff.; BGH 7.2.1984, NJW 1984, 1397 ff; BGH 14.2.1989, NJW, 1989, 1533-35.

<sup>317</sup> „Der nicht von der Zustimmung des Betroffenen gedeckte Eingriff in absolute Rechte und Rechtsgüter verletzt diese Interessen, nicht aber ein dann separiertes Selbstbestimmungsrecht des Rechtsgutsträgers“: Wagner, 2004: 1820, Rn. 663.

<sup>318</sup> Hart, 1998c: 292-293.

*legal setting enslave information to legitimizing medical intervention,*<sup>319</sup> on the other side, others (together with the medical profession) refuse the idea implicated by this systematization, that a *healing intervention has the same legal status as a stab, if not previously allowed by the patient.*<sup>320</sup>

The legal literature has underlined the inadequacy of the “Körperverletzungsdoktrin” to deal with doctor’s profession: The intervention of the doctor takes place in a situation which is already compromised by the illness; moreover, it is driven by healing purposes, therefore it should not be qualified as bodily offence on principle.<sup>321</sup> Indeed, it has been underlined that by allowing the claim for moral damage also for contract breaches, the legislator has intended to steer the future medical liability law into its natural setting, namely breach of contract (rather than tort law)<sup>322</sup>.

On the other side, the point for not distinguishing the two aspects of self-determination (legitimization of privacy invasion vs. freedom of choice in a wide sense) in court decisions has been to dam litigations based on self-determination right alone with no damage.<sup>323</sup> A recent court decision gives a formal argumentation for this position: a breach of duty to inform represents indeed an offence to the right of self-determination, but in the context of health damage, this right has a relative importance if taken separately. The court questions whether between two patients

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<sup>319</sup> See Hart 1998c: 300-301, 310.

<sup>320</sup> See for instance Giebel et al., 2001: 863. According to justice Ulsenheimer, the doctor distinguishes themselves from a stabber (“Messerstecher”) only by the information provided for consent. This opinion has been repeatedly reported in the literature as a point in the argument or for refusing the classification of medical intervention as a violation of bodily integrity. See Beller, 2000: 6-11. Wagner, 2004: 1820 RdNr 643, instead denies any ethical connotation of the offence and emphasizes the pure formal classification of this charge as bodily violation.

<sup>321</sup> See Francke, Hart, 1999: 96. Two fundamental theories have been proposed: the act theory, and the outcome theory. Following the *act theory*, no medical intervention is considered a violation of bodily integrity when it is performed in compliance with medical standards and the required level of care (*de lege artis*). Therefore informed consent plays no legitimating role: legitimation comes from the healing purpose and the conformity to professional standards, even if the outcome is not successful and leads to health damage.

Also according to the *outcome theory* the medical intervention is not a violation of bodily integrity but with the provision that no health damage occurs. Otherwise it is considered a violation of bodily integrity, which can be covered by informed consent whenever the intervention has been performed with compliance to medical standards (informed consent can never legitimize medical error). Francke, Hart, 1999: 96-97.

<sup>322</sup> „An die Einbeziehung des Schmerzensgeldanspruchs in die Rechtsfolgen vertraglicher Haftung hat der Gesetzgeber die Erwartung geknüpft, dass die *ihrer Rechtsnatur nach vertragliche Arzthaftung* künftig nicht mehr mithilfe des Deliktsrechts abgewickelt ist“. Ibid, citing the BT-Drucks. 14/7752: 15 (my emphasis).

<sup>323</sup> See also Wagner, 2004: 1848, Rn. 725. Another factor which complicates the discussion about the qualification of the duty to inform is that the self-determination doctrine would translate in a burden of proof bored by the patient. Also difficult would be the assignment of moral damages for violation of personality rights on the charge of contractual breach, notwithstanding the recent law for the modification of compensation duties (Zweitens Gesetz zur Änderung schadensersatzrechtlicher Vorschriften, 01. 08. 2002). This law has introduced moral damages also in connection to obligations, but compensation duties are limited to the goods enlisted in § 253 II BGB, and personality rights are not included in the list. See Krudop-Schol, 2005: 117, 120

injured in the same way, he who was previously adequately informed suffers substantially less than the other who lacked information.<sup>324</sup>

Also difficult is the application of § 823.1 BGB to cases where the doctor incurs in medical errors, from which nevertheless *no damage* results. According to the law, the consent covers only an intervention *lege artis*, so that in these cases a duty to inform has been breached: In these cases though, the good offended cannot be health, because there has been no damage, and it can hardly be bodily integrity, given the specific situation of medical intervention, for which a physical contact is to be considered routine.<sup>325</sup>

The considerations above recall the argumentation that contributed in the U.S. law system to the shift from “battery theory” (breach of duty imposed by the law) to the “negligence theory” (breach of professional duty) of informed consent. The distinction between the two theories is grounded on the different purposes that the information is supposed to accomplish: legitimation of the bodily intrusion in the first case, and patient’s enablement in an autonomous decision in the second.

The official justification of the duty to inform as a professional care duty rather than as a legitimation of what otherwise should be a battery comes with the Canterbury case (1972):

*True consent* to what happens to one’s self is the *informed exercise of a choice*, and that entails an opportunity to evaluate knowledgably the options available and the risks attendant upon each. The average patient has little or no understanding of the medical arts, and ordinarily *has only the physician to whom he can look for enlightenment with which to reach an intelligent decision*. From these almost axiomatic considerations springs the need, and in turn the requirement, of a reasonable divulgence by physician to patient to make such a decision possible.<sup>326</sup>

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<sup>324</sup> „Der Aufklärungsmangel stellt sich als Eingriff in das Selbstbestimmungsrecht des Patienten dar. Dieser Eingriff hat jedoch isoliert betrachtet kein Gewicht, das die Zuerkennung eines Schmerzensgeldes rechtfertigt... Dass der nicht sachgemäß aufgeklärte Patient bei Verwirklichung des Risikos stärker belastet ist als der ordnungsgemäß aufgeklärte, lässt sich nicht feststellen. Vor diesem Hintergrund ist der in dem Aufklärungsversäumnis liegende Eingriff in das allgemeine Persönlichkeitsrecht des Patienten nicht derart bedeutsam, dass die Zuerkennung eines Schmerzensgeldes rechtfertigt“. OLG Koblenz, 1. 4. 2004, VersR 2004, 1565. The OLG Jena though, in general contrast to previous and subsequent court decisions, has granted moral damages in tort also on the basis of the self-determination right alone. The argumentation provided is that the patient’s right to self-determination is always violated when the information provided is not adequate and conform to law standards, independently from further consequences that this violation might have. “Wie bereits dargelegt, entspringt das Recht auf umfassende Aufklärung dem Recht des Einzelnen auf freie Bestimmung über seine Person. Es soll ihn schützen, dass der Arzt ein ihm nicht zustehendes Bevormundungsrecht anmaßt. Dieses Recht ist *stets verletzt, wenn nicht hinreichend aufgeklärt wird. Schon dann ist die auf der fehlerhaften beruhenden Reduzierung der Entscheidungsgrundlage des Patienten einen Eingriff in seine Persönlichkeit und körperliche Integrität*. Inwieweit sich diese Pflichtverletzung dann im weiteren Verlauf der Behandlung niederschlägt, ist für diese Rechtsmissachtung ohne Belang” (OLG Jena, 3.12.1997, VersR, 1998, 588 (OLGR 1998, 35 = MDR 1998, 538). The legal literature offers different approaches to the question of the status of the medical intervention in connection to autonomy rights. For a discussion see a. o. Krudop-Scholz, 2005: 83-87; Giebel et al.: 2001: 863-68.

<sup>325</sup> Wagner, 2004, 868.

<sup>326</sup> Canterbury v. Spence, 464 F.2d 780 (D.C. Cir.1972) (footnotes omitted), cited in Faden (1986, p. 133-34), my emphasis.

With this argumentation, the court finally establishes the doctor's duty to inform not as a requirement for not incurring in an illegitimate battery, but as a consequence of the asymmetric relationship to the patient and therefore as part of his professional duty.

The difficulty in developing an information duty on the grounds of self-determination rights alone is due to the fact that whereas in the USA the prosecuted breach is a general offence of the right of privacy which comprises both bodily integrity *and* right to self-determination, in Germany the tort under consideration is restricted to bodily integrity and health, and only indirectly to the right to self-determination.

## 5.2 Professional duties and right to self-determination as freedom of choice

The fundamental change brought about by the 2nd Amendment Law of Compensation is the disentanglement of doctor's information duties from the doctrine of bodily injury (Körperverletzungsdoktrin).<sup>327</sup> The consequence is that violation of the right to self-determination through failure to provide information triggers a right to compensation independently of the establishment of a tort. In this legal setting doctor's liability arises not as a consequence of illegitimate bodily intrusion, but as a result of the expert-to-lay relationship between doctor and patient: the decision freedom of the patient is honored only if he is provided with the necessary information to perform it (information and counseling about the illness, available therapies, risks and benefits thereof, medium to long term consequences etc.). In contract liability, the damage derived from the lack of self-determination information consists in the lost chance to decide upon one's own health, independently of eventual material damage.

The duty to inform is part of the healing task implicated by the professional relationship and is aimed at guaranteeing the patient's right to self-determination in therapeutic choice as it is also constitutionally guaranteed by § 2 I GG in connection with § 1 I GG (personality rights).<sup>328</sup>

The immaterial damage of the lost decision chance refers to the decision enablement independently of the health outcome and is compensated through damage for pain and moral sufferings.<sup>329</sup>

The doctor comes to be not only the healer, who must inform about the risks related to his intervention, but also a health *counselor*,<sup>330</sup> and the information provided by the doctor does not aim to disclaim him from eventual damage as a result of residual risk, but instead must first of all *enable the patient's choice*. This is a counseling communication model whose ultimate purpose is not the patient's consent as in the "Körperverletzungsdoktrin", but rather the promotion of the patient autonomy in a

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<sup>327</sup> This solution had already been advocated a. o. by Hart, 1998c: 308 ff

<sup>328</sup> Hart, 1998c: 309.

<sup>329</sup> See Hart, 1998c: 315, f.

<sup>330</sup> For a recent discussion on the different profiles that the role of health counselor could assume see Woolf, 2005.

doctor-patient relation, structured through professional information responsibilities.<sup>331</sup> In this context, information serves the purpose of grounding a shared decision based on the different competencies of doctor and patient.<sup>332</sup> *The freedom to decide about one's own health is protected independently from the fact that health is offended.*<sup>333</sup>

## 6. Concretization of information duties in the Informed Consent model

The legal foundations underlying the IC model and the counseling model reflect in the concretization of the related information duties.

I will first present the traditional regulation as it has been inherited by the judiciary through the application of the informed consent theory, and then compare it to the desiderata entailed by the counseling communication model.

It should be however pointed out that also the judiciary related to tort liability shows a tendency to increasingly demand higher information requirements:<sup>334</sup> this could be interpreted as the perception that the informed consent model should be amended in order to adequately warrant the principle of self-determination and patient's choice.

### 6.1 Information scope

The doctor is supposed to keep updated about any new advance in medicine through scientific literature, newsletters of the health sector, the press in general and official bulletins and communications (for instance the "Rote-Hand-Brief").<sup>335</sup>

However, the duty to comprehensive and continuous updating cannot and must not translate in a duty to a total information disclosure towards the patient: this would be impossible for practical reasons, and also inadequate to the health communication purpose. The doctor is not supposed to pour out all possible risks connected to the therapy, instead he is asked to give the patient a general idea of the benefits and risks connected to the proposed therapy. As a general criterion, he must disclose the risks that can concern the patient specifically and that are relevant for his decision.<sup>336</sup>

Liability applies only to the damage, whose risk was not disclosed prior to therapy, and whose disclosure was due.

However if the doctor totally fails to give the patient a "general risk disclosure", ("Grundaufklärung"), then he is liable for *any* damage resulting from the treatment,

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<sup>331</sup> „Patientenautonomie und informationelle ärztliche Berufsverantwortung sind die zwei Seiten derselben Medaille „Kommunikation“. Es geht eben nicht nur um die Einwilligung in eine Behandlung, sondern um *Information als Voraussetzung für Entscheidungen*“: Hart 1998c: 311.

<sup>332</sup> Cfr. Hart, 1998c: 310 - 312.

<sup>333</sup> Hart, 1998c: 314.

<sup>334</sup> „Die Rechtsprechung [tendiert] zu einer ständigen Ausdehnung der ärztlichen Aufklärungspflicht, um angesichts der sich vervielfältigenden Möglichkeiten der modernen Medizin das Selbstbestimmungsrecht des Patienten zu behaupten“: Emmerich, 2006: 846.

<sup>335</sup> Francke, Hart, 1999: 31.

<sup>336</sup> BGH NJW 1980, 847; NJW 1982, 147; NJW 1985, 2192; NJW 1989, 1533; OLG Köln VersR 1997, 1491.

even if it was not subjected to information duty (“nicht aufklärungsbedürftig”). This results from the fact, that the lack of general information about the treatment invalidates consent, and therefore the resulting damage qualifies the intervention/therapy as invasion of bodily integrity.<sup>337</sup>

Informed consent is thus treated as granted towards the whole treatment (risks and benefits), and not as given in a punctual fashion for each risk disclosed by the doctor.<sup>338</sup>

### 6.1.1 Risk disclosure duty: activation criteria, quantity and form

Court sentences have detailed the risk disclosing standards. These regard the amount, content, and form in which risk information must be disclosed to the patient.

In a liability perspective, the causality condition gives an indirect but precise selection criterion: any information which can prevent a reasonably foreseeable damage must be communicated to the patient. In the case of safety information, this equates to the communication of *all* warnings and precautions, and to the promotion of compliance.<sup>339</sup> As for self-determination information, the principle of damage causality translates in the requirement of communicating information relevant for the decision underlying the consent:

1. *Magnitude*. The duty to inform is activated whenever a risk is severe, important for the life quality of the patient and specific to the therapy under consideration.<sup>340</sup> The principle of proportionality determines the amount of information to be delivered: the higher the risk, the greater is the detail and quantity of information which should support the decision.

2. *Indication*: the less severe is the illness, the more information needs to be provided about intervention and related risks: there is an inverse proportion between illness severity degree and risk information duty;<sup>341</sup>

3. *Damage relevance for life quality*: when the risk is important and relevant for the consequences on life quality, it is to be disclosed even if its frequency rate is very low.<sup>342</sup> The frequency therefore is not considered as a basis for a disclosing duty:

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<sup>337</sup> OLG Brandenburg 1.9.99 VersR 00, 1283-84; BGH 14.11.1995, NJW 96, 777; BGH 14.2.1989, NJW 89, 1533-36.

<sup>338</sup> Francke, Hart, 1999: 162.

<sup>339</sup> See for a detailed account: Krudop-Scholz, 2005: 129-132. To safety information belongs also the tailored evaluation and presentation of risks and *benefits*, as to avert therapy rejection, that could be caused by the exclusive mentioning of risks: *ibid.*: 135.

<sup>340</sup> Francke, Hart, 1999: 57.

<sup>341</sup> Krudop-Scholz, 2005: 97.

<sup>342</sup> Wagner, 2004: 1839, Rn. 705, with reference to NJW 2000, 1884: “Entscheidend für die ärztliche Hinweispflicht ist nicht ein bestimmter Grad der Risikodichte insbesondere nicht eine bestimmte Statistik. Maßgebend ist vielmehr, ob das betreffende Risiko den Eingriff spezifisch anhaftet und es bei seiner Verwirklichung die Lebensführung des Patienten besonders belastet“. See also BGH NJW, 1994, 3012; NJW 1972, 335; NJW 1980, 633; NJW 1984, 1395, 97; NJW 1990, 1528; NJW 1991, 2344; VersR 2000, 1283.

courts have recognized that incidence rates are of limited informative value for the single case: more important is the relevance for life quality.<sup>343</sup>

4. *Risk specificity*. Frequency of the risk is not a relevant dimension as for information duties, instead specificity is. Even risks which are very improbable to occur must be disclosed if they are specific to the intervention, i.e. they are known to occur in association with it, rather than for other causes.<sup>344</sup>

5. The communication of the risk frequency itself is another matter of fact, and generally is not part of the duty to inform, but it must be delivered if asked by the patient.<sup>345</sup>

6. Frequency rate must be communicated instead, as far as the possibility of *therapeutic success* is concerned, particularly when the failure rate is high.<sup>346</sup>

Furthermore, the less important is the expected benefit, the more detailed has to be any information about the risks.

7. *Information about alternatives*. A general duty to inform the patient about the therapeutic *alternatives* has not been established by judicature. This is a consequence of the principle according to which the judgment of the most suited therapeutic method to be adopted falls on the doctor.<sup>347</sup> Merely hypothetical alternatives need not to be disclosed for consent to be valid.<sup>348</sup> Some theorists adduce that a reason for this is also to be found in the general unconcern of the patient about the medical details related to his case.<sup>349</sup> This supposition needs further empirical investigation, and cannot be considered of general value.

However the judicature has established a duty to inform about alternatives, which constitute a real optional choice because of a different risk/benefit relation. Moreover the doctor is supposed to inform about alternatives in the measure that he deviates from standard methods of health care.<sup>350</sup>

8. *Urgency*: the more urgent is an intervention, the less strict is the requirement to inform. In extreme cases also the assumption of hypothetical consent can be invoked.

9. *Time*. Risk information must be delivered sufficiently in advance to allow for an autonomous and free decision without psychological pressure.<sup>351</sup>

10. *Form*. The protection of patient's safety and autonomy must not only be guaranteed through information quantity, level of detail and sufficient time for decision, but also by choosing the adequate form. In general the doctor must create the best possible conditions for an effective communication.<sup>352</sup> In general severity of

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<sup>343</sup> BGH, NJW 2000, 1784 (1785). See also Krudop-Scholz, 2005: 96-97, with reference to BGH NJW 1980, 633. and *ibid.*: 134.

<sup>344</sup> BGH NJW 1994, 3012; *Senat VersR* 1996, 330 (331).

<sup>345</sup> Wagner, 2004: 1839 Rn. 705; with reference to BGH NJW 1992, 2351, 2352.

<sup>346</sup> Wagner, 2004: 1839 Rn. 705; with reference to BGH NJW, 1991, 2342, and OLG München *VersR*, 1988, 525 f.

<sup>347</sup> Wagner, 2004: 1840, Rn. 707; 1833, Rn. 689. See also recently: BGH 15. 3. 2005 – VI ZR 313/03: JW 2005: 1718; *VersR* 2005: 836; *MedR* 2005: 599 with comments in Bergmann, 2006: 448.

<sup>348</sup> Wagner, 2004: 1841, Rn. 708; with reference to BGH NJW 2000, 1784, 1786; OLG Dresden *VersR* 2002, 440, 441.

<sup>349</sup> See for instance Wagner, 2004: 1841, Rn. 708.

<sup>350</sup> Wagner, 2004: 1842, Rn. 720. Francke, Hart, 1999: 58.

<sup>351</sup> This is especially valid for surgery interventions and related narcotic measures. BGH *VersR* 1994, 1235 ff; BGH NJW 1994, 3009; 1995, 2410, OLG Odenburg *VersR* 1998, 769.

<sup>352</sup> Krudop-Scholz, 2005: 60.

illness and therapeutic risks cannot be understated,<sup>353</sup> however the doctor must choose the most suitable communication strategy in order to promote optimal therapeutic results. An essential factor in this respect is a trustful relationship between doctor and patient. Personal communication is considered by judicature and sociologists as well as the only adequate means to establish, maintain and enhance trust. In the case of medical communication moreover, which is characterized by strong intimacy and requires empathy, face-to-face conversation is the only adequate context in which a confident communication exchange can be encouraged. It is also only through face-to-face communication, that the patient can receive adequate attention and further enquire according to his information need: this is the best means for tailored information.<sup>354</sup> Court decisions have recognized and underlined the empathic aspect and the construction of trust as compelling reasons for preferring and requiring this form of communication.<sup>355</sup>

No written pre-drafted message can substitute personal tailored information unless the communication relates to routine measures, and the doctor gives the patient the possibility to ask for further information, when needed.<sup>356</sup>

The diffusion of printed formularies for patient information is generally attributed not only to saving-time measures, but more fundamentally to the uncertainty experienced by doctors as to the legal consequences of patient information liability. The complex ramifications of information duties do not result in definite rules for risk disclosure. Under these conditions no risk communication, no matter how complete and comprehensive it might be, can constitute an absolute guarantee against liability suits. The signature of a written form should constitute a proof support in case of legal prosecution.<sup>357</sup>

However the jurisprudence does not confer this kind of document the status of a proof for informed consent: at the most it is considered as circumstantial evidence that a personal risk communication has taken place.<sup>358</sup> The fact that an information text has been signed does not mean that it has been read and understood, not to mention that the content has been discussed with the doctor. Therefore the proof value of such forms is very limited.<sup>359</sup>

11. *Tailored information.*<sup>360</sup> Information has to be tailored to the individual in relation to his risk profile (see points 1-10) and with respect to his information demand and processing capacities:

- *Information demand:* depending on several factors such as choice delegation to the physician, self-efficacy<sup>361</sup>, coping styles to bad news, and/or control desire over events, the perceived need for health information can greatly vary from

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<sup>353</sup> BGH NJW 1995, 2410, 2411.

<sup>354</sup> Wagner, 2004: 1847 Rn. 724.

<sup>355</sup> BGH NJW 2000, 1784, 1787, f; BGH NJW 1985, 1399; BGH VersR 1973, 244 (246); VersR 1985, 361 (362).

<sup>356</sup> NJW, 2000, 1784; NJW, 1985, 1399.

<sup>357</sup> Krudop-Scholz, 2005: 111.

<sup>358</sup> Krudop-Scholz, 2005: 112, with reference to BGH NJW, 1985, 1399.

<sup>359</sup> Krudop-Scholz, 2005: 112.

<sup>360</sup> BGH NJW 1984, 1807; NJW, 1984, 2629; NJW 1991, 2346; NJW 11996, 777; VersR, 2000, 1283.

<sup>361</sup> Self-efficacy is the perceived personal capacity to elaborate and make use of information in a sensitive way. See the empirical part of this work for further discussion.

patient to patient. The optimal quantity should enable participation in the decision without overloading the patient and consequently increasing uncertainty. An information overload, which, instead of facilitating a decision, loads the patient with unmanageable data, is considered as illicit as a failure to inform.<sup>362</sup> These considerations are at the basis of the principle of “gradual information” (“Stufenaufklärung”)<sup>363</sup>, according to which, information should reach the degree of granularity that is required by the receiver.

- *Processing capacities.* Education, intelligence, profession, and familiarity with the specific matter are contributing factors in the establishment of the information level that the patient should be able to elaborate for a decision.<sup>364</sup>

From a survey conducted by the Akademie für Technikfolgenabschätzung in Baden-Württemberg results that 93% of the interviewees categorizes comprehensive and comprehensible information as “very important”.<sup>365</sup> According to sociological studies, this information desire derives a. o. from the need to reduce uncertainty, plan future actions, and get reassured.<sup>366</sup>

However a gap between perceived and expressed desire has been pointed out by several studies.<sup>367</sup>

Paternalistic attitudes can therefore be the result not only of an inherited attitude of the medical profession, but also the response to the perceived expectations of the patient, when he implicitly or explicitly shows little interest in being informed about the risks connected to the illness and the therapy.

The key to the dilemma between respect for autonomy rights and compliance issues seems to be tailored information finely attuned to the information needs of the patient. Risk communication is always a double-edged weapon, which can also have counterproductive effects: the adequate risk communication strategy should therefore account for delicate issues such as those related to the effect of bad news on the receiver. The solution does not lie in a radical option for or against paternalism, but rather in the distinction between desired and undesired paternalism: or better, in a nuanced scale from a zero degree of information need (total delegation of the decision to the doctor), up to a full autonomous choice.

When the patient does not long for any participation in the decision, paternalism becomes a way to meet his desires.<sup>368</sup>

### 6.1.2 Exemption from risk disclosure duty

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<sup>362</sup> OLG Zweibrücken VersR 2000, 892, 893; Deutsch JZ 2000, 902. See also Krudop-Scholz, 2005: 101.

<sup>363</sup> See Krudop-Scholz, 2005: 94; Waller, Evans, 2003: 24.

<sup>364</sup> The judgment of such factors is a source of uncertainty for doctors, who cannot be sure that their subjective assessment of the patient’s information need and comprehension capacity does correspond to reality. On the other side, the subordination of the establishment of information quantity and level to the doctor’s opinion represents an arbitrary limitation of the information disclosure due to the patient: Francke, Hart, 1999: 130-131.

<sup>365</sup> Dierks et al., 2001: 123 f., cited in Krudop-Scholz, 2005: 46.

<sup>366</sup> Siegrist, 1981: 249; Baumann et al., 1982: 43 f., both cited in Krudop-Scholz, 2005: 46.

<sup>367</sup> See for instance: Vollmann and Helmchen, 1997: 870., cited in Krudop-Scholz, 2005: 46.

<sup>368</sup> Krudop-Scholz, 2005: 56.

For several reasons, the patient might renounce to be informed: the right not to know is part of the right to self-determination. In this case too, the doctor is dispensed from information duties. *Patient's waiver* can be explicit or implicit, but the doctor is supposed to reliably verify to what extent the patient refuses to be informed; especially implicit waiver requires strong and clear cues, that the patient does not want to be informed.<sup>369</sup>

In parallel, there are unfortunate cases where the patient *cannot* possibly give consent, because unconscious or severely injured. In these cases the doctor must account for the patient's preferences, and act consequently on the basis of a medical risk/benefit assessment.<sup>370</sup> Information about patient's values can be obtained from most proximate relatives, or by drawing on declarations of will. If no knowledge about the patient's preference is available, the doctor can intervene on the basis of so called '*hypothetical consent*': the assumption that a reasonable patient would assent to the adopted therapy.<sup>371</sup>

No information duty is contemplated for risks which are well known<sup>372</sup> or – for the same principle – towards patient who are already familiar with them because of a chronic disease.<sup>373</sup>

The information duty does not apply also in case of so called "*therapeutic privilege*"; i.e. when the foreseeable reactions to the disclosing of information would constitute an objective obstacle to the course of the therapy with no specific benefit whatsoever.<sup>374</sup> In these circumstances the two main goods underlying health regulation oppose: right to self-determination and right to health and life protection. However, according to precedence regulation for constitutional goods, primacy is granted to self-determination rights, even in case where the will of the patient seems unreasonable from a medical perspective or detrimental for his own health. Through adequate communication the doctor can nonetheless reconcile both instances and guarantee adequate warranty to both patient's health and autonomy rights.<sup>375</sup>

### 6.1.3 Burden of proof

The burden of proof for tort liability is on the doctor. Because an informed consent is what removes the illegitimacy on principle of the violation of bodily integrity, it must

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<sup>369</sup> Francke, Hart, 1999: 143.

<sup>370</sup> Wagner, 2004: 1825, Rn. 674.

<sup>371</sup> The juridical literature often confuses 'hypothetical consent' and 'alternative behavior'. In both cases the doctor has failed to provide due information, but in the former it is assumed that the patient was not possibly able to process the information; instead in the latter the patient could have processed the information but it is assumed that he would have behaved in the same way or would have made the same decision even if the doctor would have informed him adequately (hence 'alternative behavior'). The confusion might probably stem from the fact that in both cases the disclaiming function of these clauses is based on a negative counterfactual: the lack of information is not causal to damage, because its presence would have not result in a different outcome.

<sup>372</sup> Wagner, 2004: 1842, Rn. 712.

<sup>373</sup> Wagner, 2004: 1843, Rn. 713.

<sup>374</sup> Wagner, 2004: 1844-45.

<sup>375</sup> Francke, Hart, 1999: 141.

be proofed not only that the consent has taken place, but that the required information has preceded it.<sup>376</sup>

Given that causality to damage is a condition for compensation, litigations are also decided on the counterfactual argumentation about the hypothetical behavior of the patient, in case the information would have indeed been provided (alternative behavior of the doctor).<sup>377</sup> In this case the doctor must demonstrate that even by complying with the information duty, nevertheless the patient would have decided in the same way. In order to rebut this claim, the patient needs to prove, that instead, he would have found himself in a *decision conflict*.<sup>378</sup>

In the case of contract liability instead, the failure of providing adequate information is not considered as an offence to bodily integrity, but rather as negligence (“Behandlungsfehler”), and therefore it is up to the patient to prove that such a violation of standard care has taken place.

## 7. Counseling

Traditionally, liability suits for violation of self-determination information have been raised within the framework of tort liability, and within this framework counseling is not considered necessary for consent to be valid. As a consequence, courts have not provided a straightforward classification of the counseling activity. Sometimes it has been categorized as safety information – which is due to the patient in force of contractual obligations and not as a requirement for consent –; sometimes it has been considered as a separate performance.<sup>379</sup>

A court decision differentiates for instance counseling information which cannot fall into safety information from information for self-determination through the criterion that, although it would not have been material to the decision of undertaking the therapy itself (self-determination), still it would have led the patient to adopt further safety measures.<sup>380</sup>

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<sup>376</sup> Wagner, 2004: 1856 Rn. 744. NJW, 1980, 633; NJW 1981, 2002; NJW 1984, 1807; NJW, 1985, 1399; NJW, 1992, 741, VersR 1988, 525; VersR, 1990, 1852.

<sup>377</sup> Wagner, 2004: 1858, Rn. 746.

<sup>378</sup> Francke, Hart, 1999: 119; Wagner, 2004: 1858, Rn. 746 with reference to following court decisions: BGH NJW 1984, 1397, 1399; BGH NJW 1989, 1533, 1534; BGH NJW 1984, 1808, 1809; BGH NJW 1991, 1543, 1544; BGH NJW 1991, 2342, 2343; BGH NJW 1991, 2344, 2345; BGH NJW 1992, 2351, 2353; BGH NJW 1994, 2414, 2415; BGH NJW 1998, 2734; OLG Köln VersR 1999, 98, 99; OLG Brandenburg VersR 2000, 1283, 1285; OLG Oldenburg VersR 1999, 1422; 2000, 232; OLG Koblenz NJW-RR 2002, 310, 311; OLG Stuttgart VersR 2002, 1428.

<sup>379</sup> Krudop-Scholz, 2005: 69, 165-66. Court decisions: OLG Düsseldorf VersR 2002, 856, 857; BGH NJW 1987, 705; OLG Frankfurt/ M VersR 1999, 1544, 1545; OLG Düsseldorf VersR 2002, 1284 f.

<sup>380</sup> BGH 2.12.1980: NJW 81, 630-33. The sentence regards information about the success rate of a sterilization intervention for therapeutic purposes. Given that the operation was aimed at preventing pregnancy only as a means for reducing the onset of health problems, and that the consequent birth of a baby had no such damaging effects, no damage can be connected to information failure. Still the couple could have taken the sterilization *also* as a family planning measure, in which case, awareness of the success rate would have been relevant for the further decision of adopting additional contraceptive measures.

The following table presents a synoptic scheme of the legal grounds and status of different type of medical information before the changes brought about by the 2<sup>nd</sup> Amendment Law for Compensation: the counseling activity falls under contractual obligations and is not categorized as information required for consent to be valid:

### Doctor's duty to inform

Disclosure typology	Legal foundation	Content requirements	Type of offence in case of violation	Burden of proof
<p>“Selbstbestimmungsaufklärung”: Information for self-determination RISK DISCLOSURE</p>	<p><b>Remove illegitimacy of violation to bodily integrity and health offence through informed consent</b></p> <p>→ with consent patient shoulders residual risk</p>	<ul style="list-style-type: none"> <li>- Intervention description</li> <li>- Direct risks and consequences</li> <li>- Benefit probability</li> <li>- <u>Alternatives</u> (only if differ in benefit/risk profile)</li> <li>- Dangers of zero strategy (no medical intervention)</li> </ul>	<p>Breach of duty to inform – lack of informed consent (Aufklärungsfehler):</p> <p>↓</p> <p><b>tort (§ 823.1 BGB) &amp; breach of contract (§§ 278, 280 BGB)</b></p>	<p><b>Doctor:</b> Must proof that the illegitimacy on principle is cancelled by the informed consent of the patient</p> <p><b>causal connection with damage required</b></p>
<p>“Beratung” COUNSELING</p>	<p>Prevent avoidable risks when they depend on patient's <b>health choices (within and beyond the therapy)</b></p>	<ul style="list-style-type: none"> <li>- <u>Other alternatives</u></li> <li>- Instructions about the therapy and post-treatment behavior and eventual additional recommendations</li> </ul>	<p>Medical negligence (Behandlungsfehler):</p> <p>↓</p> <p><b>Breach of contract 280 BGB</b></p>	<p><b>Patient:</b> Must proof that the contractual party did not meet all professional standard required by the law</p> <p><b>causal connection with damage required</b></p>
<p>“Sicherungsaufklärung”: Safety information WARNING</p>	<p>Prevent avoidable risks when they depend on patient's <b>behavior within the chosen therapy</b></p>	<ul style="list-style-type: none"> <li>- All instructions about the therapy and post-treatment behavior</li> </ul>		<p><b>causal connection with damage required</b></p>

Figure 7: Synoptic table of doctor's information duties before the changes introduced by the 2<sup>nd</sup> Amendment Law for Compensation.

In this framework, information for consent (“Risikoaufklärung”) and counseling (“Beratung”) falls under two different categories and respond to different legal requirements.

A major point of distinction as far as the information content is concerned, is the duty to inform about alternatives: *missing information about alternatives does not invalidate the consent if these do not objectively differentiate from the proposed procedure along a standard risk/benefit assessment.*<sup>381</sup> This is precisely because the relevance of information for consent is evaluated counterfactually through causality connection with the health damage: whenever the damage could have been *equally probable* with an alternative option, then it cannot be assumed that the eventual patient's decision to opt for it would have led to a decreased damage probability. Therefore, lack of information about it is not considered causal for the damage occurred. As a consequence, alternative options which are not characterized by an

<sup>381</sup> BGH 7.4.1992 (NJW 1992, 2351).

objective difference in the risk/benefit profile need not be disclosed for consent to be valid, and falls rather under the ‘counseling’ category.

Along the changes brought about by the 2<sup>nd</sup> Amendment Law for Compensation, the doctor is liable for compensation in the case of failure to provide self-determination information also on contractual grounds. Therefore, this legal setting steers the doctor’s professional performance towards a more comprehensive activity of both health manager and counselor.

The counseling activity acquires the independent function task of warranting the patient’s enablement to make the therapeutic decision, independently of the purpose to legitimize the bodily intrusion.

Indeed, the increased need for a real counseling activity has been emphasized in recent development of professional standards for specific medicine sectors such as genetic diagnostics, transplantation medicine, procreation medicine, and biomedicine in general in Germany and across Europe, and in professional guidelines and recommendations as well.<sup>382</sup> In these contexts “Aufklärung und Beratung” (risk disclosure and counseling) represent a conceptual tandem,<sup>383</sup> where no clear terminological definition has been established in order to legally distinguish them. In fact, in these medical fields more than in traditional medicine, it is perceived that a true informed consent cannot be reached unless a thorough counseling activity precedes and accompanies the health choice. Whether the counseling task is exemplified through catalogues or defined through general clauses, the general principle underlying all guidelines and regulation referring to it is the principle of choice enablement for the respect of the patient’s right to self-determination in the most comprehensive fashion, i.e. beyond the authorization to a preselected option.<sup>384</sup>

More generally, information requirements are getting progressively higher in accordance to an increased emphasis on autonomy rights and the awareness that the quality of therapy depends both on the quality of doctor’s performance and on the decision quality.<sup>385</sup> In this respect, the decision quality is defined as a function of the accuracy of the information available and of the attention paid to the decision-maker’s preferences: “patients cannot properly weigh the benefits and harms without examining the evidence in light of personal values”.<sup>386</sup>

The stress on patient’s autonomy and empowerment has been fostered not only by ethical but also by practical considerations such as:

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<sup>382</sup> See Damm, 2006: 3-7. Special norms for the information duty in specific sectors of modern (bio)medicine are included in the Transplantation Act (§ 8 TPG: legitimacy of organ explantation); in the Transfusion Act (§ 6 TFG: risk disclosure, consent); Embryo Protection Act (§ 4 I 1 ESchG: rudimental information for consent); Medicines Act (§§ 40, 41 persons protection in clinical experiments); Guidelines for drug testing (Chapter 4, Paragraph B 1.2: informed consent); Medical Products Act (§ 20 MPG: informed consent). In biomedical contexts and in genetic medicine, counseling is considered a necessary condition for the performance of medical interventions beyond liability issues. Damm, 2006: 4. This is also reflected by the detailed prescription of information contents included in the regulation (ibid.: 5, 16). Furthermore professional codes of self-regulation also include specific counseling norms especially for the above mentioned medical sectors (ibid.: 6). In general an increased counseling need is registered in the modern medicine and in the modern society in general (ibid.: 1)

<sup>383</sup> Damm, 2006: 12.

<sup>384</sup> Damm, 2006: 12.

<sup>385</sup> Eddy, 1990.

<sup>386</sup> Woolf et al., 2005: 294.

1. Beneficial therapeutic outcome of patient participation in the decision;<sup>387</sup>
2. The increased need of knowledge management and information tutoring in the information society;<sup>388</sup>
3. Costs of the health care system.<sup>389</sup>

The evidence based medicine paradigm has translated in the persuasion that not only the doctor's decision should take into account the best evidence available, but that also the patient's choice need to be based upon all relevant evidence in order to be really informed.<sup>390</sup>

These instances have been also formalized in 2002 through a charter for the patient's right issued under the patronage of the German Federal Ministry of Health (Bundesministerium für Gesundheit).<sup>391</sup> The same ministry has also funded ten research projects focused on the identification and evaluation of methods for the promotion of patients' right to self-determination in the therapeutic choice.

Standards of medical counseling have not been legally formalized yet. It is also put into question whether communication can be regulated, and whether this regulation is constitutionally required.<sup>392</sup> However, with the changing scenarios both in the acquisition as well as in the dissemination of health knowledge among the public and the consequent addition of an uncertainty component to the insecurity already induced by the illness, there is increased awareness that the *counseling aspect of medical care gains the same rank as the traditional therapeutic job.*

## **8. The communicative status of information for self-determination in tort liability (Informed Consent)**

The influence of the legal settings on the communicative flux between doctor and patient is object of controversy in the literature: Hart claims that the qualification of the medical intervention as violation of bodily integrity reduces the doctor-patient communication to a codicil in a context determined by a paternalistic conception of

<sup>387</sup> Ford et al., 2003: 591; Epstein et al., 2004: 2359; Coulter et al., 1999: 318.

<sup>388</sup> Woolf et al., 2005: 294, 296-98.

<sup>389</sup> Woolf et al., 2005: 294; O'Connor et al. 2004. See also the recent endeavor of the IQWiG to deliver evidence based information to the patient also in the perspective of rationalizing health demand among the public <http://www.iqwig.de/gesundheitsinformation.62.html>. Additionally, the German Ministry of Health has inaugurated 31<sup>st</sup> January, 2007 a centre for independent patient counseling: "Unabhängige Patientenberatung Deutschland" ([www.unabhaengige-patientenberatung.de](http://www.unabhaengige-patientenberatung.de); [www.upd-online.de](http://www.upd-online.de)). On this occasion, the Ministry Representative for Patients, Helga Kühn-Mengel has declared: "Wer mehr Wettbewerb im Gesundheit will, der muss auch dafür sorgen, dass Patienten zu Partnern der Ärzte werden und ihre Rolle als 'mündige Versicherte' ausfüllen können": [http://www.bmg.bund.de/nn\\_605060/DE/Presse/Pressemitteilungen/Presse-1-2007/pm-31-01-07-2.html](http://www.bmg.bund.de/nn_605060/DE/Presse/Pressemitteilungen/Presse-1-2007/pm-31-01-07-2.html) (last visit: 29.5.2007).

<sup>390</sup> Steckelberg, 2005: 2; Hope, 1996. Comprehensive and balanced information from the side of the doctor is especially advocated where no option significantly outweighs the others with respect to the risk/benefit profiles or in cases of "equipose": i.e. when the doctor has no specific therapeutic recommendation: Epstein et al., 2004: 2363, 2364; Elwyn et al., 2000.

<sup>391</sup> Issued on 16<sup>th</sup> October 2002, see: [http://www.bmg.bund.de/cln\\_041/nn\\_599776/DE/Themenschwerpunkte/Gesundheit/Patientenrechte/Patientenschutz-und-Patienten-2194.param=.html\\_nnn=true](http://www.bmg.bund.de/cln_041/nn_599776/DE/Themenschwerpunkte/Gesundheit/Patientenrechte/Patientenschutz-und-Patienten-2194.param=.html_nnn=true)

<sup>392</sup> See Damm, 2006.

the doctor role.<sup>393</sup> Wagner objects that communication between doctor and patient depends on many factors but certainly not from the way legal theorists construct their case solutions.<sup>394</sup>

The next two paragraphs bring a little contribution to this debate by comparing the communicative status of information delivered for consent and of counseling information on the basis of their institutional effects.

I will recur to basic notions of speech act theory and the theory of agent communication, because they have developed a considerable explicative power for the analysis of institutional communication.<sup>395</sup>

The definition of consent given by speech act theory is:<sup>396</sup>

*“...The core principle for consenting is: to give permission in response to a request by H to do X that H does not have a right to perform without permission, but if granted will be performed by H”.*

This definition is the result of a logical analysis of the act of consent mainly devised for dealing with sexual crimes. All the factors included in this definition are also entailed by the “Körpervetzungsdoktrin”:

1. to consent is a subtype of permitting (“Einwilligung”);
2. the concept of granting a permission upon a specific request (giving a consent) includes the fact that without it, the act which is object of the request is not allowed (“Unerlaubte Handlung”: tort);
3. the purpose of asking for consent is to be allowed to do the act, which is object of the request (“Behandlung”: medical intervention).

The Informed Consent model is based on the right to self-determination as a right to jurisdiction over one’s body: the medical procedure is going to affect the patient’s

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<sup>393</sup> „Die Körpervetzungsdoktrin macht die Arzt-Patient-Kommunikation zum „Anhängsel“ einer paternalistisch konzipierten Arztrolle, indem sie die Aufklärung (nur) auf die fürsorgende Behandlung des Arztes (Einwilligung) bezieht und den Patienten nur aus dieser Sicht (die zweiseitige Kommunikationsbeziehung reduzierend) wahrnimmt“. Hart, 1998c: 310; also cited in Wagner (2004: 1829, Rn. 643).

<sup>394</sup> Wagner, 2004: 1829, Rn. 643.

<sup>395</sup> Speech acts as object of philosophical investigation can be first found in earlier works of the German philosopher and legal theorist Adolf Reinach. Following the German phenomenological tradition, Reinach investigates the ontological nature of obligations. He distinguishes between relative and absolute obligations. The obligation contracted by saying “I will bring you to the cinema” is related to the specific promise expressed in the proposition. But the obligation itself of keeping promises in general is an absolute one, which makes up the basis of the possibility of language at all: Burkhardt, 1986: 22. As a consequence, in his framework, linguistic considerations concern how it is at all possible that obligations emerge out of speech acts.

Instead, Austin’s contribution comes from the opposite perspective and lies precisely in the emphasis that saying is *also* doing. His research focus is in the means through which obligations come to be in force. Austin, John L., *How to do Things with Words* (Oxford: Clarendon Press, 1963). Searle further radicalizes the contractual and conventional aspect. See: Searle, John *The Construction of Social Reality*, (London: Penguin Press, 1995). I do not think that the two approaches are the sign of irreconcilable contradictions: it is rather a question of investigation object (communication vs. social acts in general) and disciplinary perspective (analytical philosophy vs. phenomenology).

<sup>396</sup> Cowart, 2004: 520.

body and health, over which the patient has a (constitutionally protected) jurisdiction and therefore the *authority to give consent to*.

In order to be valid consent needs to be informed, i.e. given upon knowledge of the act which is going to be performed.

However the more essential factor concerning request for consent in medical setting concerns the risk related to the intervention. The concept of consent elaborated through years of court decisions exceeds the mere permission to do the act under request, and involve the residual risk connected to that act as part of the request. The point of the request is not so much the procedure in itself, but rather the risk connected to it, because in the Körperverletzungsdoktrin, the legal consequence of a *lack of informed consent* is that the doctor is liable for residual risk.<sup>397</sup>

Asking for permission translates in a reallocation of risk: the residual risk connected to the therapy ceases to be under the doctor's responsibility, soon after he has communicated it to the patient and the patient has consented to the therapy.

Therefore communication is decisive as a distributor of responsibility and of damage liability. The table illustrates this point.

DAMAGE SOURCE:	DOCTOR'S LIABILITY IN CASE OF DAMAGE
Residual risk about which the patient has been informed	By giving his consent, the patient shoulders the risk connected to the intervention: <u>the doctor is not liable for damage imputable to residual risk for which adequate information has been provided</u> (Information = Disclaimer).
Residual risk about which the patient has <b>not</b> been informed	<b>Violation of information duty:</b> If it can be established that the missing information would have led the patient to a different decision, than the patient has the right to compensation. <u>The doctor is liable for bodily invasion (lack of informed consent).</u>
<b>Medical error</b> (avoidable risk)	<u>The doctor is always liable</u> for failing to meet professional standards of medical practice.

**Table 1: Distribution of risk along the two parameters control and information. Unavoidable risk (residual risk) does not fall under the doctor's control; therefore it must be shouldered by the patient, with the provision that he has been made aware about it prior to the therapy choice.**

*Medical consent* has two institutional effects:<sup>398</sup>

- it counts as a *removal of illegitimacy* through *permission* for the ones who gives it,
- it exempts the one to which it is accorded from *responsibility about the residual risk* associated to the object of consent.

Consequently, *information* provided for consent is contemporarily:

- the condition for consent to be *valid*,
- a *disclaimer* towards the risk communicated in it.

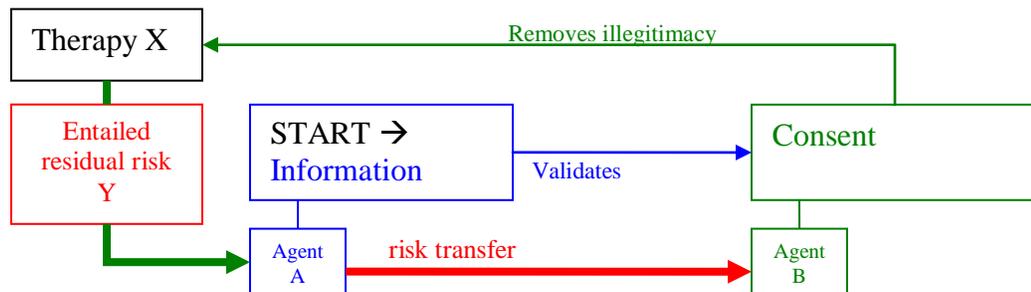
The disclaiming function is not a primitive element of consent from a communicative perspective.<sup>399</sup> It is rather an institutional construction developed in

<sup>397</sup> Wagner, 2004: 1826.

<sup>398</sup> Koyuncu speaks of a double legal nature, 2005b: 290. See chapter 3 and 4. Our terminology becomes now closer to communication rather than legal studies.

order to face uncertainty in medical performance, and generally in every technology, whose benefit is associated with some risk.<sup>400</sup>

To the duty to inform corresponds a shouldering of responsibility by the informed person towards the content of the information: If someone asks you the permission to do x, and tells you that x implicates risk y, by consenting to x, you also accept y. This dynamics is shown in the diagram:



**Diagram 1: The double legal nature (institutional effect) of residual risk information: consent validation and reallocation of risk responsibility through the legitimization provided by consent.**

Two points emerge from the graphic:

1) Informed consent consists of an *adjacency pair*: the delivery of information about the therapy and its residual risk, and the consent to the therapy. Given that the delivery of information is subordinated to consent, its communicative nature should be investigated in the direction of a request for consent rather than in the simple transfer of data.

2) The delivery of residual risk information prior to therapy has a *double institutional effect*: *consent validation and consequent reallocation of risk responsibility*, precisely as an upshot of the legitimacy to therapy provided by consent.

The communicative nature of medical information in tort liability results precisely from the communicative structure of point 1, and from the related institutional effects (point 2).

### 8.1 Informed consent as an adjacency pair

Communication acts can be profitably analyzed as commitment manipulation actions.<sup>401</sup> Commitment to a certain proposition is defined as the responsibility bearing towards the truth or the realization of the state of affairs described by the proposition.

For instance for the act of informing and requesting the following is valid:<sup>402</sup>

<sup>399</sup> See the definition of consent presented above.

<sup>400</sup> See chapter 3 § 3.3.

<sup>401</sup> Colombetti et al. 2003: 79.

<sup>402</sup> Colombetti et al. 2003: 80.

- *Information*: by informing that “a” is the case, agent x makes a commitment relative to the receiver, that “x” is the case. The institutional effect of informing is the commitment to the truth of the information delivered;

- *Request*: by requesting “a” to y, agent x puts the receiver y in a state of pre-commitment, where the receiver can decide to commit himself to “a” by accepting the request, or do not commit himself to “a” by declining the request.

Basic commitment manipulations are:<sup>403</sup>

- 1) make commitment (ex.: “inform” or “promise”);
- 2) cancel commitment (ex.: “retreat”);
- 3) make precommitment (ex.: “request” or “ask”);
- 4) accept precommitment (ex.: “consent”);
- 5) cancel precommitment (ex.: “refuse”).

From the commissive point of view, “consent” equates to the *acceptance of a pre-commitment*.

Therefore, for the adjacency pair principle, information provided for consent should not simply be categorized as “information” (make commitment) but rather as a “request” (make precommitment).

*The institutional effects of the consent to this request, however is not exhausted by the permission to carry out the therapy but also by the reallocation of the related residual risk. Therefore, because of this second institutional effect, the delivery of information for consent is not only a request for permission, but also amounts to a disclaimer about residual risk, in that the consent given by the patient results in the assumption of responsibility about the delivered risk (commitment).*

*Because in tort liability, respect of the right to self-determination is subordinated to health damage, the disclaiming function of medical information is in this context preponderant and from a legal point of view primary.*

## **9. Communicative status of information for self-determination in contract liability (counseling)**

Self-determination information provided within contractual obligations should foster the patient’s right to an autonomous choice *per se*, independently of eventual damage. In the case of information duty violations, the moral damage is represented by the lost decision chance or choice impairment. Therefore, medical information is also aimed at risk transfer but does not reduce to this function. The professional information duties regulated by contract liability are rather aimed at enabling the patient’s decision on the basis of adequate and relevant information. This translates in an information duty which should warrant the right to self-determination as a *right to be enabled to choose*.

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<sup>403</sup> Colombetti et al. 2003: 81.

The duty to inform is based on the asymmetric epistemological situation between doctor and patient, on the doctor's responsibility over the medical procedure, and on the patient's right to decide over his body and health.

This approach changes the relationship not only from a paternalistic one to a contractual one, where duties and responsibilities are consciously shared among the parts involved. More importantly, it extends the contract duties from the mere material beneficence of removing or alleviating the disease to the fiduciary aspect of health counseling for a personal informed decision.

The counseling model confers a specific meaning to risk communication which differs from the informed consent model. In the counseling model the point is not to ask for permission, but rather to enable the patient's decision. This is not a two-steps communication exchange (asking for permission; granting it), but rather a common sharing of competences: the doctor informs the patient about benefits and risks connected to the procedure and to eventual alternatives; the patient discloses his preferences and then a decision takes place.

Consequently, the reason for which the patient shoulders the risks connected to the medical procedure differ in the two settings: in the IC model, the patient is supposed to shoulder the risks connected to the procedure *because, having being informed about them, he is aware of them*; in the counseling model, rather than merely consenting to a proposal, the patient *actively participates in the decision*, and shoulders eventual damage because he takes on co-responsibility for the medical treatment, and bears the risks which do not fall under the medical control.

The IC model focuses on the patient's authority over his body, the counseling model (or Shared Decision Making model) on his right to decide about health issues.

The most evident difference between the two models of medical communication can be illustrated by referring to the duty to disclose therapeutic alternatives.

## 10. Information about alternatives

The duty to inform about alternatives imposed by tort liability is restricted to options with an *objective* difference in the risk profile. In fact the only dimension considered in litigations about failure to disclose alternatives is whether the damage would have been significantly *less probable* if the patient would have chosen the alternative option, which was not disclosed to him.

This is a direct consequence of the fact that compensation for information failure is related to *damage causality*, rather than to *violation of self-determination*. In fact only those alternatives, which would have presented a lower damage probability, are procedurally relevant for classifying information failure under violation of bodily integrity (§ 823.1 BGB). Instead, alternatives with a similar risk profile need not to be disclosed because they present quantitatively the same risk. The doctor is not supposed to disclose in detail all available alternatives and to justify his choice.<sup>404</sup> Failing to provide this type of information *does not invalidate consent*.<sup>405</sup>

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<sup>404</sup> Heilmann, 1990: 1518.

<sup>405</sup> BGH 11.5.1982 (NJW 1982, 2121-22); BGH 19.11.1985 (NJW, 1986, 780 = VersR 1986, 342); BGH 8.5.1990 (NJW 1990, 2929); OLG Nürnberg 27.5.2002 VersR 2003, 1444; OLG Dresden 17.5.01, 2002,

With the exceptions of few court decisions<sup>406</sup>, the same is valid for options, which indeed have a different risk profile, but are not available in the health care structure in which the doctor operates. Some court decisions legitimate failure to inform about alternative technologies by resorting to the argumentation that the minimal difference in risk probability does not require disclosure duty, because not all newest medical devices can be available in every health care structure as soon as they enter the market. As long as the older technologies comply with medical standards, it does not constitute a violation of information duty, not to inform about the new alternatives.<sup>407</sup> The argumentation is fallacious in that, indeed not every health technology can be part of the diagnostic or therapeutic equipment offered by a health structure, but it belongs to the patient's self-determination sphere to choose to go in another health center, where the technology is available, or to stay where he is and be content with the older one. But in order to be able to decide between these options he must have been informed about both: it is constitutionally illegitimate to deprive him from the beginning of this information. The patient must be informed about all concretely possible alternatives.<sup>408</sup>

The IC model represents a strong limitation of the patient's freedom of choice: there could be in fact options which, even if objectively equivalent with respect to risk magnitude/probability, nevertheless could be perceived as different from the patient either because he has different feelings towards the types of risks involved, or because his system of preferences leads him to favor an option rather than another. However he will not be informed about them, just because they do not differ quantitatively in the risk probability dimensions, or the small risk difference does not justify disclosure duty:

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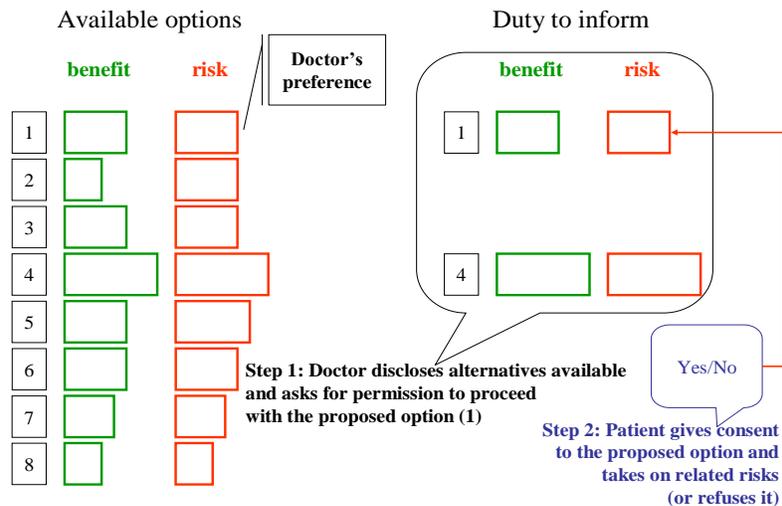
VersR 02, 440-41. Also a recent contribution emphasizes this deficiency in the German regulation of Patient information: Beller, 2000: 8. Beller cites a. o. a study on disclosure habits in German settings (FIGO Committee for the Study of Ethical Aspects of Human Reproduction. Guidelines regarding informed consent. *Frauenarzt* 1997: 36) according to which the uterine carcinoma is removed through surgery or treated with radiotherapy depending on whether the first physician consulted is a gynecologist or a radiologist. The different early and late complications are seldom communicated to the patient though.

<sup>406</sup> BGH 12.2.1974, VersR 74, 752-54.

<sup>407</sup> BGH VersR 1984, 470 ff.; 22.9.1987 (NJW 1988, 763-65).

<sup>408</sup> It is also insufficient to stipulate the duty to answer to patient's questions about alternatives, because this would already presuppose some awareness about them. This awareness cannot be taken for granted for all patients: Francke, Hart: 1999: 125-126.

## Informed Consent Model

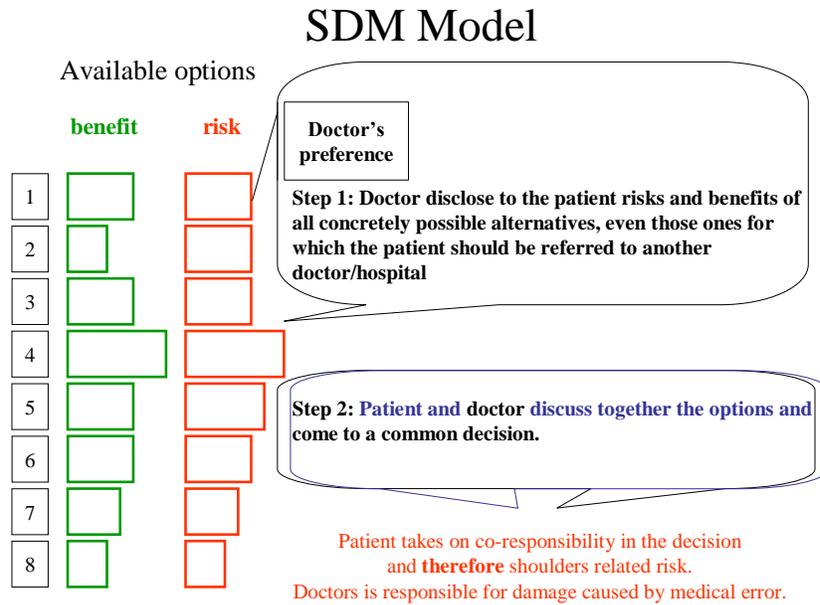


**Figure 8: Informed consent model: only alternatives, which significantly differ in the risk profile, must be disclosed to the patient. The patient gives than his consent to the proposed option and thereby takes on responsibility for the related risks.**

The picture shows that only the doctor’s favorite option is disclosed to the patient, and eventual concurrent alternatives, whenever they have a significantly different risk/benefit profile. The patient’s task limits to accept or refuse the proposal. The decision is left to the physician, and is only marginally integrated with the patient’s values and preferences – subjective utility connected to different aspects of different modus operandi is substituted by an (objective) standard assessment.<sup>409</sup>

The shared decision making model instead accounts for those aspects of the decision related to patient’s personal preferences and risk attitude. This requires that *all* available and realistically feasible options be discussed between doctor and patient, and that *thereafter* a decision be commonly made.

<sup>409</sup> „Sonst aber darf der Arzt, wenn keine Umstände entgegenstehen, davon ausgehen, dass der Patient, der von sich aus nicht weiter nachfragt, seiner ärztlichen Entscheidung vertraut und nicht eine eingehende fachliche Unterrichtung über spezielle medizinische Fragen erwartet; diese kann er in der Regel als Nichtfachmann ohnehin nicht beurteilen“ BGH 11.5.1982 (NJW 1982, 2122). „es versteht sich von selbst, dass es dem Patienten stets unbenommen bleibt, den Arzt über etwaige neue und überlegene, noch nicht überall zur Verfügung stehende Behandlungsmöglichkeiten zu befragen. Dann hat der Anspruch auf eine vollständige und wahrheitsgemäße Auskunft“ BGH 22.9.1987 (NJW 1988, 765). See also: BGH 19.11.85 (NJW 1986, 780 = VersR, 1986, 342); OLG Celle 17.3.1986 (VersR, 1987, 591); BGH 24.11.1987 (NJW 1988, 765); BGH 22.2.2000 (NJW, 2000, 1788-89); OLG Karlsruhe 7.6.2000 (VersR 2001, 860); OLG Dresden 17.5.2001 (VersR 2001, 440-41); OLG Frankfurt 14.1.2003 (VersR 2004, 1053) with another nuance but with the same conclusion OLG Naumburg 5.4.2004 (VersR 2004, 1461): “Die zivilrechtliche Haftung für Aufklärungsversäumnisse knüpft an das Postulat an, dass die ärztliche Behandlung über das medizinische Anliegen hinaus auch dem personalen Anspruch des Patienten gerecht werden muss ... d.h. dass die ärztliche Entscheidung ... auch den Entschluss des Patienten als personalen Faktor einbezieht. ... Zur Aufklärung über die Art des Eingriffs gehört u.a. dann auch eine Aufklärung über Behandlungsalternativen, wenn eine echte Alternative mit gleichwertigen Chancen, aber andersartigen Beanspruchungen des Patienten bzw. Risiken für den Patienten bestehen”. See also Francke, Hart, 1999: 124-126.



**Figure 9: Shared decision making model: all concretely possible alternatives are disclosed to the patient. Doctor and patient discuss them together and come to a common decision. The Patient takes on co-responsibility in the decision and therefore shoulders the related risk.**

The discussion of the healing perspectives and uncertainties is a necessary condition for a real participation in the therapeutic choice which cannot be reduced to a “yes or no” answer after the simple transmission of information.<sup>410</sup> It is understood as a sort of emancipation process towards “patient empowerment” and as an assumption of *co-responsibility* at the same time.<sup>411</sup>

## 11. Summary and conclusion

This chapter has analyzed the institute of informed consent and the recent evolutions in the field of therapeutic communication in the German legislation with the purpose of providing the background for evaluating the legal status and communicative nature of PL information.

The institute of informed consent responds to the need for warranting the patient’s right to self-determination. However it is severely in that the right to self-determination is reduced to a *jurisdiction over one’s own body*.

In the communication model presupposed by the institute of informed consent, information serves uniquely the purpose of making consent valid, and therefore results in a two-step process where the doctor asks for permission to invade patient’s bodily integrity through surgical or therapeutic intervention, and the patient grants it. Residual risk is shouldered by the patient, because he has been made aware of it through risk disclosure.

<sup>410</sup> Krudop-Scholz, 2005: 60.

<sup>411</sup> Krudop-Scholz, 2005: 57, 58.

The right to self-determination as a right to choose calls instead for a richer model of risk communication, the Shared Decision Making model, where the purpose of doctor's information is to enable patient's therapeutic choice and a common decision is taken on the basis of patient's preferences and doctor's expertise. Residual risk is shouldered by the patient, because he has co-participated in the decision, and therefore takes on the risks, which are out of the doctor's control.

The 2<sup>nd</sup> Amendment Law for Compensation brings a relevant contribution to the steering of doctor-patient communication towards a SDM model, through the explicit protection of the right to self-determination *per se*, independently of health injury.

The following chapter is devoted to investigate the interplay between doctor's and product information. I

The upshot of this analysis is a clear illustration of the responsibility distribution among pharmaceutical firm, doctor, and patient resulting from risk disclosure.



## 4 The legal status of PL information

### 1. Safety protection and self-determination information in pharmaceutical therapy

The context in which the doctor practices his profession is characterized by several sources of uncertainty. In the pharmaceutical therapy the first source of uncertainty is represented by the treatment itself, and its *interaction with the patient's organ system*. Therefore safety depends not only on the product but also on its right use.

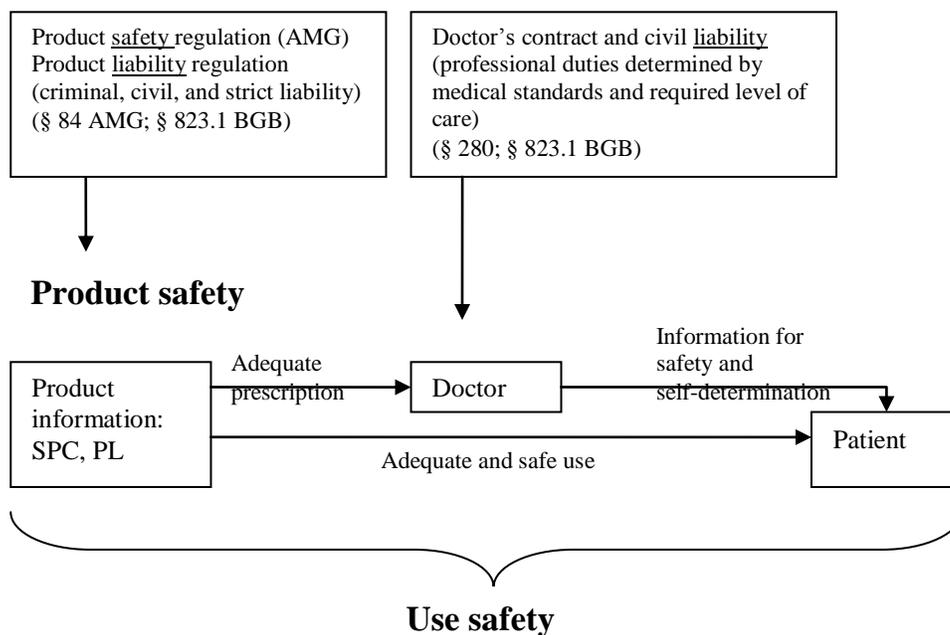
*Product safety* is guaranteed preventively by safety regulation and by civil and criminal liability in the form of pecuniary sanctions or imprisonment. *Use safety* is warranted by doctor's compliance to professional standards of prescription and is based on the product information.<sup>412</sup>

Product information therefore contributes to safety both by allowing the doctor a risk/benefit evaluation based on detailed scientific data, and by warning the patient of possible product risks.

Product information takes the form of SPC (Summary of Product Characteristics) for the doctor and of PL (Patient Package Leaflet) for the patient. The second is a simplified synthesis of the first, specifically tailored to the lay user. The diagram shows the synergy of doctor's and product information in therapeutic safety:

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<sup>412</sup> Hart, 2003: 603.



**Figure 10: Pharmaceutical safety as the result of product and use safety: the role of information.**

Product safety is protected through norms regarding risk prevention and liability (they have been presented in chapter 1 and 2 respectively). Use safety is the result of product safety, adequate prescription (doctor's professional duty) and of the patient's adequate use upon correct and complete information through both product instruction and doctor's recommendations.

As can be observed from the graphic, the production and distribution of pharmaceuticals is subject of both safety and liability norms, whereas the doctor's activity is only regulated by liability norms: a corresponding "safety" regulation for the doctor is lacking,<sup>413</sup> but an equivalent function is covered by prescription directives, guidelines and recommendations, and generally by the requirement of compliance to medical standards.

Therapy information by the doctor aims both at safety and decision autonomy, product information by the pharmaceutical firm is regulated within safety norms but is also characterized by autonomy components in that it is also object of liability regulation. In this respect PL information is also the basis for informing the patient about unavoidable – "residual" – risk (self-determination information).<sup>414</sup>

As a consequence, the patient is addressed by two distinct information sources, both accomplishing safety and self-determination purposes, but meeting different requirements of risk communication.

This chapter is devoted to product information delivered by the pharmaceutical company, especially in the form of package leaflets, its interplay with doctor's information, and the discussion about its legal status as a liability distributor of pharmaceutical risk.

<sup>413</sup> Hart, 2004: 470.

<sup>414</sup> Hart, 2003: 603.

## 2. Use safety and residual risk

Safety regulation cannot guarantee absolute risk-freeness of the pharmaceutical product, but only a general positive risk/benefit relationship, therefore each drug is a potential chance and risk for the patient's health at the same time.<sup>415</sup> Through risk prevention norms, safety regulation aims to guarantee the highest possible level of safety, without inhibiting the production and distribution of pharmaceutical technology. The risk margin left as a price for the beneficial effects expected is therefore the result of a general evaluation, which needs further consideration prior to prescription to the single user.

With the general safety judgment ("Unbedenklichkeit") about a pharmaceutical *product*, it is yet said nothing about its safe *use*.<sup>416</sup>

For each individual, in fact the same product can be associated to a different risk/benefit evaluation depending both on product characteristics, and on the patient condition and predisposition to side effects. The more severe is the illness, the higher is the allowed toxicity level of the drug; the higher is the patient's predisposition to side-effects specific to the drug under consideration, the more negative becomes the individual risk/benefit assessment. A drug which has a *general positive risk/benefit evaluation* can show a *negative risk/benefit profile for a specific user*. The prescription of such an *approved drug* is considered medical error. The doctor's task consists in minimizing the therapeutic risks by choosing the product which best suits the patient's risk profile for the required indication.

Pharmaceutical firms are liable for product safety; the doctor is liable for therapy safety.<sup>417</sup> This implicates that he is supposed to keep updated about the level of safety of the pharmaceutical offer, and to make the optimal choice under the perspective of an individual evaluation of the risk/benefit profile tailored to the patient.<sup>418</sup>

The medical prescription is the means through which the doctor acts as a filter between the products offered by the pharmaceutical market (and the general risk/benefit evaluation associated to them) and the single patient with his personal risk profile. The doctor must "translate" the general risk assessment into a concrete one, and evaluate on this basis whether the concrete risk for the individual exceeds the expected benefit.<sup>419</sup> The doctor should assess a tailored risk prognosis by integrating statistical data registered in product information with patient's information as acquired through anamnesis and other diagnostics.<sup>420</sup>

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<sup>415</sup> Franke, Hart, 1999: 59-60.

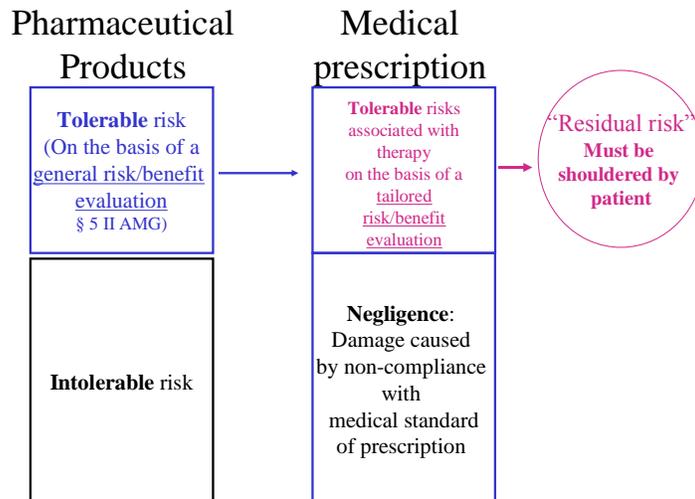
<sup>416</sup> Krudop-Scholz, 2005: 147.

<sup>417</sup> Hart, 2003, 603. Francke, Hart, 1999: 60.

<sup>418</sup> Francke, Hart, 1999: 51.

<sup>419</sup> See Hart, 2003: 605.

<sup>420</sup> In Bayesian terms, this equates to updating the risk probabilistic hypothesis delivered by frequency data related to the product on the basis of patient's data. For the Bayesian approach regarding the interpretation and updating of probabilistic data with reference to pharmaceuticals see chapter 6.



**Figure 11: The distribution of residual risk in the pharmaceutical therapy**

The drug profile is evaluated in connection to the patient considered for prescription, and only if it results in a positive *individual* risk/benefit evaluation, is the drug considered adequate for therapy. Therefore side-effects which are considered tolerable in consideration of the product benefit *in general* (drug residual risk) can be judged intolerable when related to a particular therapy for a *specific user*. This can be the result of several factors: the severity of the illness can be of such a level that does not demand for dramatic measures, or the patient seems to be sensitive to the most severe side-effects, etc. It is the doctor’s task to judge all these aspects and decide whether the individual residual risk represented by the drug can be justified by a corresponding benefit.

Medical sciences have greatly developed in diagnosis expertise and technologies; and also pharmacology has greatly increased its battery of research instruments and methods.<sup>421</sup> Still, the healing course and therapeutic (medium to long) term effects depend on such a complexity of factors that no guarantee of success can be provided in advance. Genetic predispositions, health history, compliance, drug sensitivity, and possible interferences with other drugs a. o. constitute a network of risk factors, whose end-effect cannot be predicted.

The threshold line between product faultiness and product “residual risk” is based on a general risk/benefit evaluation (§ 5 II AMG); the threshold line between prescription error (medical malpractice) and therapy “residual risk” is established through reference to medical standards.

In analogy to drug residual risk, therapy residual risk is the risk considered unavoidable in order to reach the benefit promised by the treatment under

<sup>421</sup> The progress in diagnostics has not been accompanied by equal developments in etiology (understanding why illnesses emerge at all) and therapy: only 20% of currently known diseases are treated causally, the remaining 80% is treated symptomatically (Krudop-Scholz, 2005: 43).

consideration. It is not covered by liability compensation, because it is considered the exchange price to be paid for the received benefit.<sup>422</sup>

Avoidable risk instead is represented by damage which can be prevented either through doctor's compliance to medical standard, and/or through patient's compliance to doctor's instructions.

In all cases communication has an essential role in distributing responsibility about the risk associated to the therapy.

Because residual risk must be shouldered by the beneficiary party, product information responds not only to safety instances, but also to the requirement of self-determination. The Summary of Product characteristics (SPC) – product information for the doctor – should help the doctor determine whether he wants to dare the prescription; less clear is the role of PLs, because the patient principally receives self-determination information from the doctor.

### **3. Pharmaceutical risk communication to the patient**

The patient is directly addressed by risk communication fundamentally through two channels: the pharmaceutical firm (PL), and the doctor.

Moreover, the legal system in which patient information takes place is guided by two fundamental principles: safety and decision autonomy. Safety regulation protects life and health; self-determination norms are the corollary to autonomy rights.

As a consequence, both doctors and PL information are supposed to warrant the best possible protection of health, while at the same time allowing for an autonomous decision.

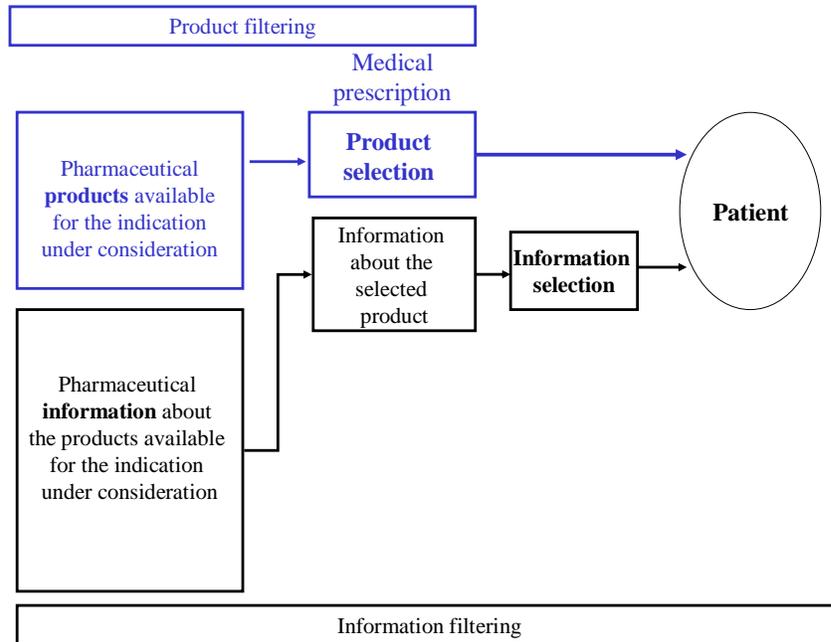
Both information generators have a specific collocation within the legal system. Nevertheless, little consideration has been devoted by the literature to the consequences of their interplay, and ultimately to the role of PL in this setting.

The doctor is supposed to inform the patient about the risks connected with the therapy: this information forms the basis of his correct behavior during the therapy (safety information), and of his decision whether he prefers to undergo the therapy or the illness risks (information for self-determination).

The double filtering task, which the doctor is supposed to accomplish – tailored product prescription *and* information –; can be represented through the following diagram:

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<sup>422</sup> Francke, Hart, 1999: 115.



**Figure 12: Double filtering tasks in medical prescription: product and information selection**

The choice of a pharmaceutical therapy entails several specific tasks in comparison to the surgical intervention: the doctor is responsible for effectiveness and safety of the individual therapy, and is supposed to prescribe the most suited product to the single user. This implicates an overall knowledge of the pharmaceutical environment (pharmaceutical characteristics and benefit/risk profiles of products relevant for the indication under consideration): on the basis of this knowledge and the information concerning the patient, he must select the product which optimizes the individual benefit/risk profile of the patient.<sup>423</sup> In a conservative therapy, for instance, an erroneous prescription (wrong indication, dosage or duration) constitute a breach of professional duties.<sup>424</sup>

A second filter is then constituted by the selection of information to be delivered to the patient for participating in the decision.

Also information must be selected and tailored to the individual. First of all, not all the potential risks affecting a therapy or a medical intervention are foreseeable; secondly also predictable risks cannot and need not to be completely communicated in the context of doctor-to-patient consultation. Just the contrary: the information must be attuned to the need and capacity of the receiver and eventually foster a shared decision making process.<sup>425</sup>

<sup>423</sup> Francke; Hart, 1999: 51.

<sup>424</sup> Product quality and prescription quality constitute the two pillars of a dual drug safety system. Hart, 2003: 603 ff.

<sup>425</sup> Deutsch, 2003: 102. BGH NJW 1971, 1887; NJW 1974, 1422 (1423); NJW 1983, 333. See chapter 3 §§ 4, 8 on the theoretical distinction between counseling and informed consent model.

However, in the case of pharmaceuticals, the doctor is not the only source of information for the patient. Safety law establishes that the drug be accompanied by detailed product instruction (§ 11 AMG), and liability regulation foresees sanctions for damage, originated by information faultiness (§ 84 I 2 AMG; § 823.1 BGB). In reality, the official motivation provided by the legislator in introducing the requirement of product information within AMG is not related to self-determination and freedom rights, but rather to safe use.<sup>426</sup>

Nonetheless, because of tort liability norms connected to product instruction, the function of this information goes beyond the mere indication of caution measures, and assumes the function of a disclaimer for residual risk.<sup>427</sup>

Since 1986, through the distinction between expert and lay information in the second AMG amendment, product information directly addresses the patient. But because of the general duty to inform imposed principally on the doctor, the legal status of this information is still not clearly assessed.<sup>428</sup>

The first discussion of this issue has been generated by two recent court decisions,<sup>429</sup> which have aroused heated debates among legal theorists. The sentences implicate that PL or written information can surrogate doctor's risk disclosure. They explicitly declare that it is part of the patient's self-responsibility to become knowledgeable of the information contained in the PL, and therefore discharge the doctor from damage liability.<sup>430</sup>

A third sentence has been emanated recently and reestablishes the doctor's primary duty to inform and the subsidiary function of PLs.<sup>431</sup>

These contradictory views on the role of PL within the therapeutic communication context demand for a deeper investigation of its legal status and communicative function.

#### *Sentence LG Dortmund 6. 10. 1999*

The case concerns the information about thrombosis risk related to the intake of a mixed compound of estrogen and progesterone. The patient, a paralyzed woman, was suffering under menstrual disturbs in the form of uninterrupted bleedings. Soon after three days of therapy she experienced beneficial effects. The therapy was not interrupted after these first signs of healing, and the patient went on taking the drug according to the prescription. Unfortunately, after two weeks she felt strong pains at the link leg, and recovered in a community hospital, where it was established, that she had been hit by thrombosis.

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<sup>426</sup> Reasons grounding the government bill of the 3<sup>rd</sup> AMG amendment. Printed in Kloesel, Cyran, *Arzneimittelrecht Kommentar § 11 AMG*. V. Hart, 2003, 605.

<sup>427</sup> Koyuncu, 2006: 345.

<sup>428</sup> Hart, 2003: 605.

<sup>429</sup> BGH NJW 2000, 1714 and LG Dortmund, MedR 2000, 331. Through these sentences, the relationship between PL and doctor's information has been addressed for the first time: "Erstmalig wurde von Rechtsprechungsseite das Verhältnis von ärztlicher Aufklärungspflicht und Packungsbeilage thematisiert und definiert": Krudop-Scholz, 2005: 21.

<sup>430</sup> LG Dortmund 6. 10. 1999, MedR 2000, 331: "Den Patienten trifft die Pflicht, sich durch verständliche Beipackzettel über die Risiken einer Medikation zu unterrichten" also cited in Rehman, 2003: 92.

<sup>431</sup> BGH 15. 3. 2005, NJW 2005, 1716 (1718).

The patient had not been informed about this eventuality by the doctor, and did not read the PL, where an explicit warning was devoted to this risk.<sup>432</sup>

The court has rejected the law suit against the doctor for breach of information duty and has grounded this decision on the assumption that, the patient could and should have got notice of the thrombosis risk through the PL. The court acknowledges that the patient must be informed about the risk connected to the therapy, but it is denied that this task must exclusively be performed by the doctor. Given that the pharmaceutical company includes in the drug packaging an information text specifically directed at the patient – in fact § 11a AMG explicitly separates expert from patient information – than, risk information takes place also through the PL. *The doctor is obliged to provide risk information to the extent that it is not already delivered through the PL. With the due exceptions (aggressive drugs, incomplete information), the PL substitutes doctor's information.*

A recent sentence has instead re-established the primacy of the doctor over the PL as an information source for self-determination:

*Sentence BGH 15. 2. 2000*<sup>433</sup>

The sentence concerns a case of polio vaccination, for which the consent is not considered invalid by the prosecutor, even if not obtained through a face to face conversation. The case does not specifically regard PL information, but, in parallel with the preceding one, the doctor is discharged from liability, because written standard information is considered sufficient for consent to be valid.<sup>434</sup> This form of communication is however considered legitimate and adequate under the provision that the therapy is familiar to the patient because of its routine character. *It is explicitly recognized that information consent formularies cannot substitute risk communication through the doctor, in that the doctor is supposed to verify, whether the patient has taken knowledge of the formulary content.* The patient must be granted the possibility to eventually ask for further information and clarification.

*Sentence BGH 15.3.2005*<sup>435</sup>

This is the last sentence to date, which concerns the relationship between doctor and PL information. The case is more complex than the preceding ones, because the damage (thrombosis) has not been caused by the drug itself (an hormone preparation), but by the drug interference with nicotine, the eventuality of which had not been sufficiently stressed by the doctor in the consultation phase.

Information about correct behavior belongs to safety information, however the courts underlie that the doctor has to respond also for failure to provide information

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<sup>432</sup> „Die Einnahme von Geschlechtshormonen ist mit einem erhöhten Risiko venöser und arterieller thrombo-embolischer Krankheiten ... zum Beispiel venöse Thrombosen ... verbunden. Dieses Risiko kann durch zusätzliche Faktoren ... erhöht werden ... Bei längerer Bettruhe kann die Gefahr einer Blutropfbildung (Thrombose) bestehen.“ From the sentence acts: LG Dortmund, MedR 2000, 332.

<sup>433</sup> BGH NJW 2000, 1787.

<sup>434</sup> BGH NJW 2000, 1784 (1788).

<sup>435</sup> BGH 15. 3. 2005, NJW 2005, 1716 (1718).

for self-determination, drawing on the argument that this failure would equate to a lack of informed consent.

As for the charge of lack of informed consent, the court of first instance and the Court of Appeal (OLG Rostok) equally reject it, on the basis of two elements:

1. *decision conflict*: from the prosecutor's examination it results that if adequately informed about the risks connected to the interference between drug and smoking, the prosecutor would have stopped smoking, therefore she would have taken the *same decision* of making the therapy (she would have not found in a decision conflict);
2. *PL information*: the PL did contain warnings which emphasized the risk of thrombosis. Moreover the PL explicitly cautioned from smoking precisely the risk group to which the patient belonged to (smoker and 30 years old or more).<sup>436</sup>

The Supreme Court rejects both points as follows:

1. the prosecutor's assertion that, if adequately informed, she would have stopped smoking rather than decide not to take the drug, does show a lack of decision conflict, but also that the missing information has been *causal* to the damage: had the risk been adequately disclosed, the patient would have behaved consequently and the *damage would have not occurred*;
2. the information contained in the PL is not sufficient for patient's self-determination. Precisely in the case where the patient belongs to a specific risk group, and where the risk is typical for the prescribed drug, special attention is needed for making sure that the patient is aware about damage which can be determinant for their life quality. Especially in the case of wrong behavior such as smoking addiction, the doctor cannot rely on the supposition that the patient will read and follow the instructions contained in the PL. The simple intimation, that "pill and smoking do not stand each other" does not display with sufficient force the entity of the health consequences implicated by the interference of treatment and smoking habits.<sup>437</sup>

With reference to this sentence it can be noticed, that the information would have not been material to the decision of taking the drug or not, but to *the decision of quitting smoking*. Therefore the lack of information has been causal to the damage rather as a failure of therapeutic information (safety information), than as a lack of information for autonomous decision.

The reason for which lack of informed consent gives right to compensation is that the patient must suffer a damage that was not taken into account during therapy choice because not disclosed by the doctor.

The difficulty lies here in the fact that, indeed the risk had not been disclosed and therefore could not have been possibly taken into account in the risk/benefit

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<sup>436</sup> „Bei Raucherinnen, die östrogen-gestagenhaltige Arzneimittel anwenden, besteht ein erhöhtes Risiko, an zum Teil schwerwiegenden Folgen von Gefäßveränderungen (z.B. Herzinfarkt, Schlaganfall) zu erkranken. Das Risiko nimmt mit zunehmendem Alter und steigendem Zigarettenkonsum zu. Frauen, die älter als 30 Jahre sind, sollen deshalb nicht rauchen, wenn sie östrogen-gestagenhaltige Arzneimittel einnehmen“.

From the sentence acts: BGH 15. 3. 2005, NJW 2005, 1716.

<sup>437</sup> BGH 15. 3. 2005, NJW 2005, 1717

evaluation prior to decision. However, it was not a risk pertaining to the drug alone, but to the simultaneity of drug taking and smoking (“and” cause).

Therefore, in this case the information would have been material to the decision, only under the condition that the patient would have had reserves in choosing the treatment, precisely because of this information. Yet, the lack of decision conflict, as it results from the examination, does not allow for this interpretation: the missing information can be therefore classified only as safety information, whose omission does not constitute a lack of informed consent.

The flaw contained in this sentence reflects the increased tendency to interpret counseling information as self-determination information.

The diversity of judgmental positions on this matter in general echoes the vagueness of the concept of self-determination pointed out at the end of the previous chapter and translates in flexible interpretations of the information requirements for consent validity.

The role played by product instruction (PL) nearby doctor’s information comes therefore to be all the more vague and difficult to assess.

Two questions underlie in general the definition and evaluation of the PL legal nature in the therapeutic context:

- 1) the legal task(s) which it is supposed to accomplish;
- 2) the congruity of PL texts to the prescribed tasks.

#### **4. The legal status of PL information**

##### **4.1 Regulation of PL information**

Besides the existence of unavoidable risk affecting drugs safety, this risk is also difficult to avert because the pharmaceutical product is particularly opaque. No external cues (form, taste or color) can help the user recognize product faultiness. Moreover its inscrutability is greatly enhanced by the complexity of its chemical structure. This is the reason why product information concerning pharmaceuticals has paramount importance and a special place in pharmaceutical regulation.<sup>438</sup>

The history of pharmaceutical regulation shows the increasing importance assigned by the legislator to product instruction as a source of safety information nearby the doctor. The result is that even if the PL is a vehicle of communication between pharmaceutical company and patient, its information and textual design is predominantly due to the legislator, to whom – more than to the company – the merit or the blame of a high/low product information quality should be ascribed.

In the origin, no information at all was provided together with the product. Drug regulation before 1961 did not even prescribe information to the doctor, which was facultative and consisted generally in a list of chemical composition and therapeutic indications (often written in Latin). With AMG 1961 a labeling duty is introduced, and 1976 AMG stipulates the obligation to accompany the product with specific

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<sup>438</sup> Krudop-Scholz, 2005: 148.

information:<sup>439</sup> § 11 AMG<sup>440</sup> prescribes that pharmaceutical products as defined by § 2 AMG must be accompanied by a package insert with the title “Information for use” (“Gebrauchsinformation”), whose content must be continuously updated along the state of medical and pharmaceutical knowledge.

The norm establishes content and sequence of the information, which must include: name of the product (§ 11 I 1 Nr. 1); components (nr. 2); form of intake (nr. 3); drug category or effect type (nr. 4); name of the pharmaceutical company and producer (nr. 5); indications (nr. 6); contraindications (nr. 7); precautions (nr. 8); interferences with other drugs or food (nr. 9); special warnings (nr. 10); drug dosage and therapy duration according to patients groups (nr. 11); countermeasures in case of overdose, intake omission, or early therapy interruption (nr. 12); *all* side effects and related countermeasures, plus the indication that the patient is asked to refer to the doctor any drug reaction not enlisted in the PL (nr. 13); date of expiry (nr. 14)<sup>441</sup>; last information update (nr. 15).

In particular, specific risk groups must be separately addressed when medical/pharmaceutical knowledge requires special precautions for them (for instance risk incidence is significantly higher). It must also be warned against misuse and abuse by clarifying eventual consequences, when this can represent a concrete possibility. This also includes eventual alert about attention decrease and reduced driving capabilities.

Additional information – except for advertising messages – is allowed insofar as it is distinctly separated from official information (§ 11 V AMG); it is forbidden to tone down risk information through additional messages: additional information must be clear and objective (“sachlich”).<sup>442</sup>

The following diagram illustrates the sources of information from which SPC and indirectly PL, derive their content:

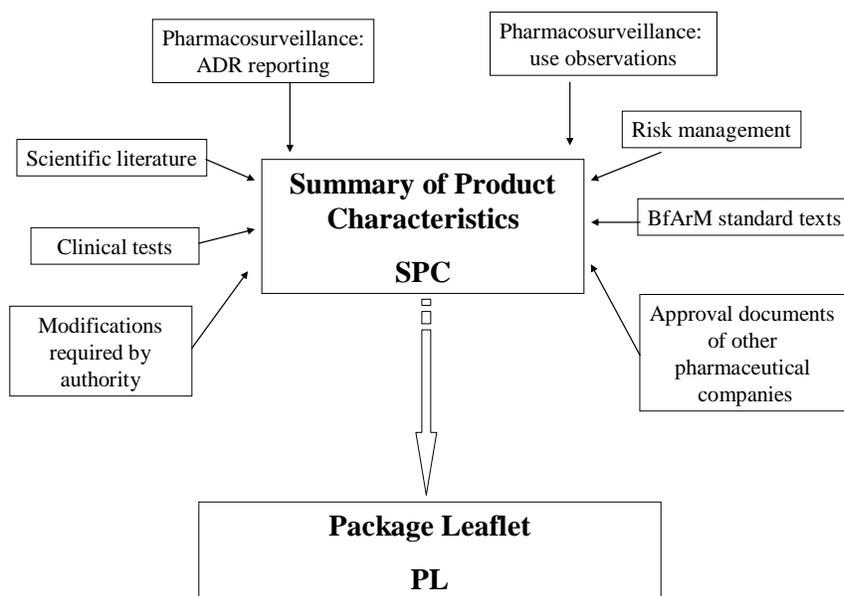
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<sup>439</sup> The 1976 German Medicines Act follows in this respect §§ 13 – 20 of the Council Directive 65/65/EEC and §§ 6 – 7 of the Council Directive 75/319/EEC according to which the inclusion of package leaflet shall be obligatory. For more details see a. o. Krudop-Scholz, 2005: 148-151 and Holz-Słomczyk, 2006.

<sup>440</sup> § 11 AMG is the national implementation in the German safety system of the European guideline 92/27/EEC.

<sup>441</sup> For plasma derivatives § 14a AMG prescribes the indication of the plasma-blood.

<sup>442</sup> Rehmann, 2003: 99, Rn. 16.



**Figure 13: Information sources and contributors to SPC and PL content. Source: Blasius, 2005: 62.**

The factors contributing to SPC and PL information are integrating part of the risk management and prevention system. This is a result of the high value conferred by safety regulation to risk communication (see chapter 1). The PL text must comply with the exemplar provided as part of the documentation for approval (§ 22 VII AMG) and any modification must be promptly notified to and approved by the authority (§ 29 I 2a); the authority can also directly influence PL information by ordering the addition of special warnings (§ 28 II nr. 2 AMG).

Safety norms of product instruction are also ratified on a liability level:<sup>443</sup> AMG sanctions the circulation of pharmaceuticals without product instructions (§ 97 II 5 AMG) and violation to information duties and scientific updating is also sanctioned through appeal to compensation charges regulated by civil norms of liability (§ 84 I 1 nr.2 AMG).

Precisely liability norms related to product instruction and regulating the responsibility distribution of residual risk confer PL information the status of information aimed at patient's autonomy in the evaluation of the risk associated to the therapy,<sup>444</sup> in analogy to the information for self-determination provided by the doctor about residual risk.<sup>445</sup>

This is especially valid for information about adverse reactions, which are explicitly defined in § 4 AMG as the undesired side-effects possibly produced by drug intake (residual risk). Given that unavoidable risk must be shouldered by the patient in case

<sup>443</sup> See also Koyuncu, 2006: 347; 2005b: 295; Blasius, 2005: 62.

<sup>444</sup> Heitz, S. 2004: 271.

<sup>445</sup> See Koyuncu 2005b: 291.

he has been previously informed about it, this information comes to acquire the status of self-determination information.

Another element confirming the legislator's intention to assign pharmaceutical product instruction also the value of information for decision is point 13.1 of the 1994 BfArM recommendations for PL information, where it is suggested to indicate whenever possible the frequency of side effects, in order to facilitate the patient in his risk estimation.<sup>446</sup>

Also court decisions have soon established the duty of pharmaceutical product information as a requirement determined by the user's right to self-determination. In the Contergan sentence, the distribution into the market of pharmaceutical products, which are presumed to cause damage, has been compared to an invasion of bodily integrity.<sup>447</sup> The responsibility to inform the user (doctor and patient) derives from the established or presumed dangerousness of the pharmaceutical product, and the consumer's *right to decide*, whether to undergo the risk connected to it or not, in face of the expected benefit.<sup>448</sup>

Therefore, along the distinction between avoidable and residual risk, and the role assigned to PL information within medical therapy, the communicative function of PL information with regard to drug consumer is twofold:

- 1) instruct the reader as to the measures to be undertaken for averting avoidable risks associated with misuse (safety information);
- 2) disclose residual risk unavoidably connected with drug use, as to provide the drug consumer with risk and benefit data for an informed decision (information for self-determination – informed consent).

PL information follows the same principles and rules illustrated for the liability regime regulating doctor's information duty.<sup>449</sup> As a consequence, the congruity of PL texts to their institutional task depends on their capacity to promote safety and foster an informed consent.

## 4.2 Legislator's initiatives for readability improvement

The patient's involvement in the therapeutic decision is indirectly stressed by the legislator's efforts towards readability improvement and user-friendliness. These are based on a long-lasting tradition in textual analysis and linguistic studies.<sup>450</sup>

The requisite of readability derives from the regulation teleology itself and is also been explicitly required by § 11 I 1 AMG<sup>451</sup>, which prescribes that information must be delivered in comprehensible German and in readable form.

Both at European and at national level PL content, language and layout have been submitted to severe scrutiny and revision.

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<sup>446</sup> “die Häufigkeit bei allen Nebenwirkungen, bei denen es möglich ist, [soll] in der Packungsbeilage angegeben werden. *Damit soll dem Patienten die Einschätzung des Nebenwirkungsrisiko erleichtert werden*“. Cited in Scheu, 2003: 705-06 (my emphasis).

<sup>447</sup> LG Aachen, 18.12.1970, JZ, 71: 515.

<sup>448</sup> LG Aachen, 18.12.1970, JZ, 71: 515.

<sup>449</sup> For details: Krudop-Scholz, 2005: 123-134; Francke, Hart, 1999: 133-136.

<sup>450</sup> See next chapter for a brief overview.

<sup>451</sup> Besch, 2000: 70.

In Germany, through the 3<sup>rd</sup> amendment to the AMG in 1988 the competent authority has established the use of model texts (“Mustertexte”). Standardization has also concerned the terminology for frequency classification of adverse drug reactions, which goes back to 1991.

With the 5<sup>th</sup> amendment to AMG in 1994, the European Directive 92/27/EEC is definitively implemented in the national law. The [92/27/CEE](#) directive (31. 3. 1992) represents a milestone in the development of pharmaceutical labeling. It provides a detailed list of information contents that the PL text must cover (particularly at point 3 of art. 7 and in art. 8) and invites to a closer connection with the layman medical background (the notion of “health literacy” is explicitly mentioned).

In 1998 [“A Guideline on the readability of the Label and Package Leaflet of Medicinal Products for Human Use”](#) has been emanated as a valid companion to an enhanced patient information quality. The document presents a set of examples and provides a guideline for testing PL readability.<sup>452</sup>

The European Readability Guidelines have been recently enforced through the 2004/27/EC directive and implemented nationally through 14<sup>th</sup> AMG-amendment<sup>453</sup>. These order the performance of readability tests for PLs as part of the procedure for drug approval. Tests should examine following parameters: readability, patient-friendliness, and easiness to find relevant information. With this amendment the legislator increases the company’s responsibility in the improvement of text-design and information management, and generally legally ratifies the readability requisite independently from conformity to the standard texts laid down by authority.

However several questions arise as to the competence of the lay reader in understanding not only the meaning of the information provided in PLs, but more importantly the (medium or long-term) health implications entailed by a specific therapy. Moreover the frequency terms with which risk information is delivered (incidence rate of side-effects) raises the question of the interpretation of probabilistic information and its contribution to a personal therapeutic decision.

Also recently the BfArM has organized a seminar for investigating the state of the art as for PLs readability and patient friendliness.<sup>454</sup>

The lecturers have stressed that readability and especially patient-friendliness does not reduce to the translation of medical jargon into common language: 44% of the PL in circulation are by now compliant with the European Readability Guidelines, but this does not mean that they are patient-friendly.<sup>455</sup> Consumer sovereignty and decision autonomy does not only depend from reliable and comprehensive

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<sup>452</sup> More on this guideline in chapter 5 § 3.

<sup>453</sup> § 22 VII, 2 AMG in the 14<sup>th</sup> AMG-amendment declares: “Der zuständigen Bundesbehörde sind bei Arzneimitteln, die zur Anwendung bei Menschen bestimmt sind, außerdem die Ergebnisse von Bewertungen der Packungsbeilage vorzulegen, die in Zusammenarbeit mit Patienten-Zielgruppen durchgeführt wurden.” This integration is due to § 61 I of the modified European directive 2001/83/EC.

<sup>454</sup> [http://www.bfarm.de/cln\\_042/nn\\_599148/DE/BfArM/Publikationen/Praesentationen/060215-Dialog.html](http://www.bfarm.de/cln_042/nn_599148/DE/BfArM/Publikationen/Praesentationen/060215-Dialog.html) Bonn, 15.3.2006.

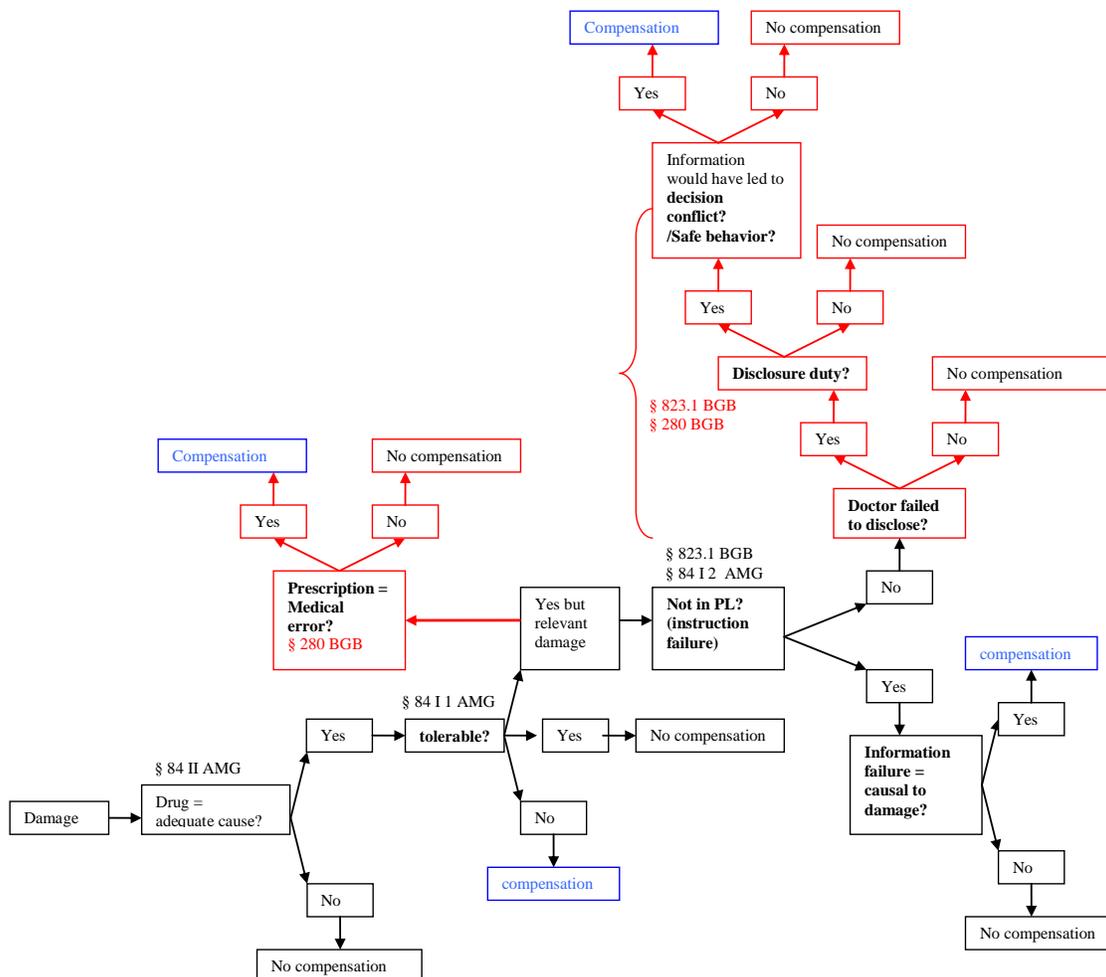
<sup>455</sup> Buchberger, 2006: 35-36

information. Readability and *usefulness* of information to the user is as important as complete and truthful communication.<sup>456</sup>

Overviews of established readability tests have been offered and new methods proposed.<sup>457</sup> In general it is suggested to conceive PLs not as isolated information supports but as a part of a communication framework. Moreover the presentation of drug benefits should compensate the disclosure of risks, so as to prevent frightening effects.<sup>458</sup>

### 4.3 Responsibility spheres for pharmaceutical damage

In order to better understand the role of risk communication within the liability framework, I present a synoptic scheme which integrates doctor's liability (red) and company's liability regulation (black).



**Figure 14: Algorithmic scheme of liability compensation for instruction failure in case of health damage (red: doctor's liability; black: pharmaceutical firm's liability).**

<sup>456</sup> Nink, Schröder, 2006: 2.

<sup>457</sup> Fuchs, 2006. See also Fuchs, 2005, Fuchs et al. 2003; 2004.

<sup>458</sup> Reimann, 2006: 17.

The scheme outlines main norms regulating pharmaceutical liability as they have been presented throughout chapter 2 and 3. The conditions for damage compensation are:

1. medical error (erroneous prescription);
2. or intolerable damage;
3. or, if tolerable according to the general risk/benefit evaluation, it is considered not irrelevant and
  - a) *product information has failed to warn against it* even if it was a risk under information duty (either as safety or as self-determination information);
    - and, the information failure has been *causal to damage*: the patient would have decided/behaved in a different way
  - b) *or, the doctor has failed to warn against it* even if it was a risk under information duty (either as safety or as self-determination information);
    - and, the information failure has been *causal to damage*: the patient would have found himself in a *decision conflict/would have followed a safe behavior*.<sup>459</sup>

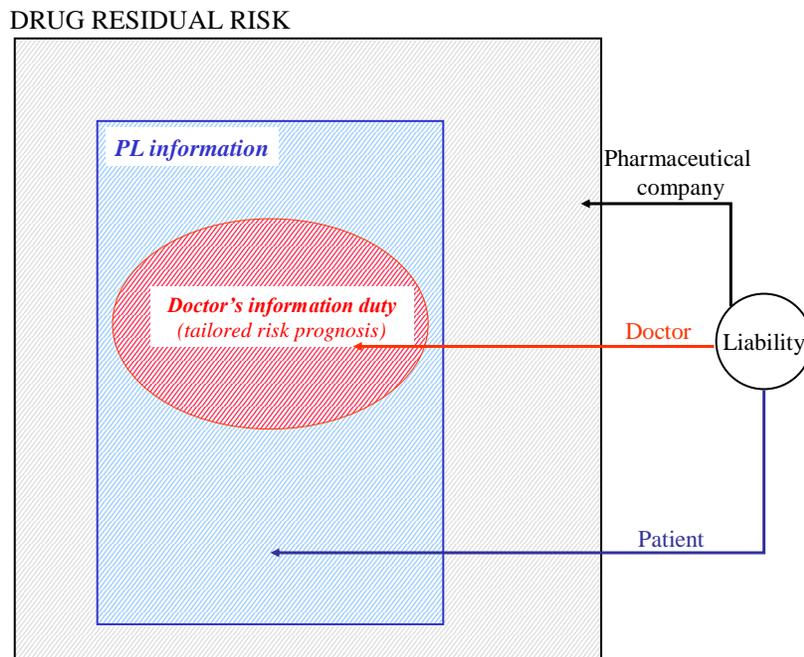
The liability role of PL emerges for all risks which are mentioned in the PL, and must not be disclosed by the doctor for information duty: these risks fall entirely in the realm of the *patient's responsibility*.

Therefore, the detailed information which cannot be provided by the doctor must be acknowledged and taken into account by the drug user. In this sense **all** the information included in the PL is relevant from a liability perspective.

The following diagram illustrates responsibility distribution for drug residual risk as it is configured by risk information liability:

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<sup>459</sup> The condition of causality for PL information vs. the requirement of decision conflict for doctor's risk disclosure have a remarkable impact in the procedural context. In this respect PL information is rather comparable to product information (ProdHaftG) than doctor's information. See Deutsch, 1989: 856, for a discussion of the legitimacy of this procedural setting. Charges related to the assessment of consent validity are decided upon psychological causality, which cannot rely upon deterministic computations but is rather based on the probabilistic evaluation that an instruction would have changed the behavior/decision of the reader or not. In the special case of pharmaceuticals, all the more when prescribed by the physician, the condition required to the patient that the information would have induced him to make another decision seems a challenge which is impossible to satisfy.



**Figure 5: Liability distribution for residual risk among pharmaceutical firm, doctor, and patient. The patient is called to shoulder all the residual risk mentioned in the PL, whether or not belonging to the realm of doctor's information duty.**

Given that the doctor is obliged to give all relevant safety information, there would be no safety instructions in the PL, which are not covered by the doctor's information liability ("Sicherungsaufklärung"); instead not all possible residual risks are part of the doctor's information duty, but only a tailored selection of drug side effects must be given to the patient in order to respect the patient's right to self-determination. The analysis of liability distribution provided by figure 5 shows that the remaining residual risks not covered by the doctor's information duty fall in the patient's responsibility.

Consent to the doctor equates to a global approval to therapy. Detailed information, which cannot and need not be disclosed by the doctor is also part of the consent and is provided by the PL. By taking the drug, the consumer accepts also the risks enlisted in the PL warnings and not mentioned during consultation.

Whenever damage follows, which do not result from prescription errors, and the mention of which was not part of doctor's professional duties, the patient has no right to compensation, if they are included in PL information.

Therefore, PLs have a specific role in the distribution of liability related to pharmaceutical residual risk.

#### 4.4 Pharmaceutical informed consent

A first problem hindering the qualification of PL information as information for consent is related to formal questions regarding the procedure of consent giving. Conservative treatments such as pharmaceutical therapies are generally decided in the

consultation and begin only after buying the drug in the pharmacy. Consent is given to the doctor in the surgery, and PL information is generally acquired after the decision has already been taken (just a moment before drug intake). This raises questions as to its binding force. Furthermore, for the same reason, the doctor is not legitimated to accomplish his information duty by simply referring the patient to the PL.<sup>460</sup>

It has been recently advocated to solve some of the formal questions related to the legal nature of PL information by creating a special IC model for pharmaceutical therapy as distinguished from the classical IC model developed around cases of surgical interventions.<sup>461</sup> The justification for creating the special institute of *pharmaceutical informed consent* derives from two main reasons:

1. In surgical interventions, not only the therapeutic decision, but also its execution is in the doctor's sphere, whereas in the pharmaceutical therapy, the doctor has no direct influence in the cure.<sup>462</sup>
2. Also from a legal point of view, the task of informing the patient about the risks connected to the treatment is not only performed by the doctor, but also by the pharmaceutical firm through the PL.<sup>463</sup>

The two points are interconnected, in that the patient is called to actively participate in the therapy success both behaviorally and also by taking notice of product information which is directly addressed at him. Co-participation in the therapy equates to an assumption of responsibility both as for compliance to doctor's instructions (point 1), and as to compliance and therefore acquisition of PL information (point 2).

Because the PL content does not limit to safety information and special warnings, but also include information about residual risk, the co-participation requirement translates in an assumption of responsibility for this risk when it has been adequately communicated.

As an objection to the point according to which, consent as already been provided during consultation, it is asserted that, precisely for that reason, the classical IC model should be modified and reconfigured. Because PL information comes on its own, when the doctor's responsibility sphere has been left, but before drug intake, then consent should be subdivided in two phases:

1. *preliminary consent to doctor's prescription* during consultation;
2. *concluding consent to the drug* by taking it.<sup>464</sup>

Information for consent to be valid comes in the first phase from the doctor and in the second phase from the PL.

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<sup>460</sup> Hart, 2003: 606.

<sup>461</sup> Koyuncu, 2006: 344 ff.; 2005b: 295 ff.

<sup>462</sup> Koyuncu, 2006: 343, 344.

<sup>463</sup> Koyuncu, 2006: 343.

<sup>464</sup> Koyuncu, 2006: 344; 2005a: 76; 2005b: 291 ff.

This setting stresses patient's responsibility in taking notice of PL information. From the fact that information failure must be causal to damage follows that the patient must have taken notice of it: whenever this does not happen, than no right to compensation can apply even if the information was faulty. In analogy to the implicit or explicit waiver for doctor's information, failing to read PL, while taking the drug, can be considered as a waiver towards pharmaceutical information delivered from the pharmaceutical firm. This implicates, in case of damage, the renunciation to compensation.<sup>465</sup>

Although the pharmaceutical informed consent model provides a technical contribution to the clarification of liability litigations related to the conflict of responsibility between doctor, pharmaceutical firm and the patient, nevertheless it does not touch deeper problems affecting the congruity of PL information to the task of enabling an autonomous choice. These problems are inherent to its actual contribution to lay health decision making.

#### **4.5 *Prima facie* objections against PL information as a basis for informed consent**

The use of PL information as a tool for patient's participation and co-responsibility in therapeutic decision faces however diverse problems, both from the formal and from a substantial point of view.

Main objections raised against PL information are the following:

1. *Incomprehensibility of technical language and lay incompetence in dealing with pharmaceutical information.* This aspect has been addressed in several occasions by the legislator. However both linguistic and empirical studies continue to emphasize the low readability level of PL texts and their reader unfriendliness.
2. *Lack of risk information tailoredness.* The basis for any decision under uncertainty, as it is therapeutic choice, is an evaluation of the different options available in consideration of the risks connected to them and the beneficial consequences.<sup>466</sup> A rational choice presupposes a comparison of benefits and risks weighted by the concrete possibility of occurrence. An abstract probability, say 1:10<sup>6</sup>, derived from statistical surveys, is of little value for someone considering the eventuality of incurring in a certain risk. It is precisely the doctor's task to translate statistical data into a reliable prognosis for the individual. Only he has an overview over patient's organic constitution, health history and other therapies in course, additional medications, all essential information for assessing reliable risk estimation

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<sup>465</sup> Koyuncu, 2006: 346. Koyuncu 2005a: 79 qualifies this situation also as contributory negligence („Mitverschulden“): this however can only be applied to the safety aspect of product information. For self-determination information, it should be better categorize failing to read PL information as waiver (renouncement to risk disclosure).

<sup>466</sup> See second part of this work for an introduction to decision theory.

about the general risks connected to the drugs. In this respect, the PL cannot possibly substitute him.<sup>467</sup>

PL information grounds on a toxicological-statistical concept of risk, whereas doctor's information is based on a tailored evaluation of therapeutic risk, which is the adequate information for the individual decision.

Hart underlines the safety aspect of product information within a framework which guarantees product quality and product safety through information to the doctor (therapy safety) and to the patient (use safety). The self-determination aspect instead is necessary mediated in this framework through doctor's risk disclosure. The PL cannot substitute the doctor as a source for self-determination information, in that the principle of self-determination requires that the individual is made knowledgeable of *his personal* risk/benefit profile, whereas product information is necessary general and abstract.<sup>468</sup> A decision can be considered autonomous, only if made on the basis of personally relevant information.<sup>469</sup>

Therefore, it cannot be considered valid a consent given on the basis of information, which does not allow a personal estimation of the risks and benefits concretely implicated by the therapy:<sup>470</sup> Consent is valid in the measure that the patient is aware of (short to long term) consequences and implications of his choice.<sup>471</sup>

Therapeutic courses of the same pharmaceutical product differ substantially in function of illness severity, patient's drug sensibility, etc. Therefore relevant information for decision can be very different from case to case even if the drug is the same. This is not only valid for dosage and duration or generally safety information, but also for the disclosure of risks.<sup>472</sup> It is indeed precisely the doctor's task to provide the patient with a tailored estimate of the types of risks, among those listed in the PL, which might concern him, and with what probability.

### 3. *Conflict between the doctor's and the patient's risk/benefit evaluation.*

If PL information is given some legal value within therapeutic decision, than the question arises as to what contribution it should bring.

If the PL brings an autonomous element to patient's decision, than it should do it by providing him with a different basis for choice, than that provided by the doctor (risk/benefit assessment). This brings a contradiction within the decision process. Either should the patient rely in the doctor's risk/benefit assessment; or else make a personal risk/benefit assessment on the basis of PL information, perhaps also different from the doctor's one. In the first case, the contribution of PL information

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<sup>467</sup> See Koyuncu, 2005b: 292; 2005c: 108. Hart, 2003: 605 ff.

<sup>468</sup> See Hart, 2003: 605; Krudop-Scholz, 2005: 156. See also Stöhr, 2006: 148.

<sup>469</sup> "Selbstbestimmt ist die Entscheidung dann, wenn die aus der Sicht des Patienten entscheidungsrelevanten Informationen zur Verfügung stehen": Hart, 2003: 605. Information relevance for decision jointly depends on three factors: the information desire of the specific patient, the information typically expected by the standard patient, and a general information ("im Großen und Ganzen") about risks which are specific to the treatment, and can have significant consequences for the patient's life quality. (Hart, 2003: 605).

<sup>470</sup> Krudop-Scholz, 2005: 160.

<sup>471</sup> Krudop-Scholz, 2005: 162: „... nur derjenige wirksam in einen Eingriff einwilligen kann, der sich dessen Bedeutung und Tragweite bewusst ist“.

<sup>472</sup> See Krudop-Scholz, 2005: 157-158.

is equal to zero; in the second case, the eventual difference between personal and doctor's risk/benefit assessments might lead to non-compliance.<sup>473</sup>

4. *Information about alternatives*: as mentioned in the preceding chapter, doctor's information about alternatives is limited in the informed consent model to options with an objective difference of risk/benefit profile. This constitutes a limitation in comparison to the counseling model. However, product instruction is exclusively limited to informing about the product to which the PL is enclosed. Any comparative information is totally lacking.

This results in an *exasperation of the IC model yes/no dynamic*: if consent to doctor has been given with little or no knowledge of alternatives, consent to PL is given exclusively with information related to the prescribed product. As Wolz puts it: „When the user has it (PL) in his hands, than a decision about a specific treatment has already been made. Alternative drugs are not available or only with difficulty, so that often the decision reduces to a choice between taking this pharmaceutical product or not ... *Even optimal designed PLs cannot warrant the user an adequate ground for decision*”.<sup>474</sup>

5. *Risk information overload*: The list of side effects notoriously exceeds the relevant amount of risk information for the single user. In general it can be said that given the high preponderance of risk information<sup>475</sup> in relation to data about benefit, any decision-maker should decide not to take the drug. Obviously this is not the intent of the legislator, and also the reader reasons that in some way the risk he is exposed to should not surpass the benefit.

On the other side, the information provided cannot be simply neglected as totally irrelevant. In fact, PL information is generally declared as highly important by drug consumers:<sup>476</sup> the tension between the sensation of information unmanageability and the high legal value results in contradictory attitudes towards this form of pharmaceutical information.

The main difficulties lie indeed in selecting items of the information which are personally relevant and material to the decision. This can be a source of paralyzing uncertainty or non-compliance, when it does not lead to the general refusal of PL information.<sup>477</sup>

This is also reflected in empirical data about drug consumption: each year 100 tons of pharmaceuticals for a value of 500 Mio. Euros go into the garbage. It is estimated that 1/5 to 1/3 of the prescribed drugs are thrown away without even opening the blister.

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<sup>473</sup> In this respect non-compliance can be considered as the result of the conflict between the patient's perception of doctor's authority and his perception of the PL's institutional value as a vehicle of information endorsed by the responsible authority.

<sup>474</sup> Wolz, 1988: 15, 16: „Hat der Verbraucher erst einmal in der Hand, so ist die Entscheidung für ein bestimmtes Medikament bereits gefallen. Alternativpräparate werden nicht oder nur unter Schwierigkeiten erreichbar sein, so das oft nur die Entscheidung zwischen Einnahme und Nichteinnahme dieses Arzneimittels bleibt ... Auch inhaltlich optimal gestaltete Gebrauchsinformationen garantieren also nicht den Entscheidungsspielraums des Verbrauchers”.

<sup>475</sup> There are PLs with more than 80 side-effects: Grandt et al., 2005: 511.

<sup>476</sup> Nink, Schröder: 2005: 31

<sup>477</sup> See Krudop-Scholz, 2005: 159-162.

Most of these are treatments against chronic illnesses, as for instance high blood pressure: this can be explained with the fact that users cannot estimate their benefit, because they do not feel any direct effect, and on the other side they have reservations in taking the drug for a long period because of the side effects listed in the PL.<sup>478</sup>

In general the objections address two aspects of PL information:

- a. Its contribution to
  - i) Informed consent;
  - ii) Therapeutic safety;
- b. Its effects on the consumer's confidence in the therapeutic decision (compliance).

In order to provide a unitary account of these aspects, PL information will be investigated in the following chapters as peace of information embedded in a decisional context, precisely within the tools offered by Bayesian theory.

This methodological choice is justified by the fact that Bayesian theory is the privileged discipline in order to account for *decision making under uncertainty*.

In fact, the general question underlying the above mentioned points is that most of the information contained in the PL is difficult to decipher, even when literally comprehensible, because the patient is not capable to judge, whether he will be concerned by it or not, and what would concretely be the consequences for his life quality.

In this respect, all main components of Bayesian theory (the theory of knowledge updating through probabilistic induction – Bayesian theorem – the theory of decision optimization through maximization of the expected utility; and the theory of information value) are relevant to our research.

In this specific framework, this approach provides the instruments for analyzing PL information:

- as a basis for knowledge updating (probability of side effects occurrence) for a risk/benefit assessment about the drug;
- as a support for decision optimization based on the expected reward of taking the drug vs. not taking it;
- finally, its perceived value can be estimated as a function of its expected contribution to decision optimization.

## 5. Summary and conclusion

This chapter has been devoted to the examination of the interplay between doctor's and product information and to display the role of PL information within liability regulation.

Doctor's duties comprise drug use safety (optimization of risk/benefit assessment for the *individual* patient) and selection of adequate information for patient's safe use and autonomous decision.

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<sup>478</sup> Bronder, Klimpel: 2001.

PL information integrates doctor's information with detailed therapy instructions and complete disclosure about residual risks. These are to be taken into account by the patient when undertaking the cure. As a consequence of the liability clause related to product information, PL acquires the legal status of information for self-determination.

As for the problems advanced to this categorization, some scholars propose to change the IC model inherited from surgical intervention into a two-phase IC model, where the patient consents to the prescription during consultation, and to the drug by taking it.

This liability setting however exasperates the IC model, which is already blamable in doctor-to-patient communication with its yes/no dynamic. The patient is not provided with a comparison of possible alternatives, but only with full information of just one product, unrelated to any other.

This setting is also critical because, a two-phase consent entails that the patient should, at least on principle, be put in the situation to question the decision already taken with the doctor on the basis of a risk/benefit assessment made personally on the basis of PL information (or by integrating doctor's with PL information). In this sense, PL information represents rather a "decision interference", and this is precisely what is lamented about with reference to non-compliance.

In general consent should be reached "voluntarily, knowingly, and intentionally".<sup>479</sup>

PL information should be therefore evaluated on the benchmark of its contribution to choice awareness. In this respect, it is fundamental in any analysis of PL information, to investigate its contribution to an informed decision. Particularly, in order to analyze whether PL texts are adequate to accomplish their institutional task, a comparison is required between the decision model implied by the legislator and the concrete decision environment specific to therapy choice.

The following parts of this work are concerned with the communicative and epistemic nature of PL information, as well as with the cognitive and behavioral aspects related to PL information processing.

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<sup>479</sup> Kleining, J. (1982) "The Ethics of Consent" in K. Nielsen and S. C. Patten (eds). *New Essays in Ethics and Public Policy* (Canadian Association for Publishing Philosophy: 9-118, quoted in Cowart, 2004: 497.



## **PART II**

### **Communication and Decision**



## 5

# Communicative status of PL information

*In the performance of an illocutionary act  
the speaker performs the subsidiary act  
of expressing the propositional content  
and this act we will call the propositional act.  
A propositional act is an abstraction from the total illocutionary act  
in the sense that the speaker cannot simply express a proposition  
and do nothing more.*

John R. Searle & Daniel Vanderveken, Foundations of Illocutionary Logic, 1985.

### 1. PL information and residual vs. avoidable risk

The legal analysis of PL information has identified two tasks imposed on this type of product instruction, namely safety information and information for self-determination (informed consent).

The following part of the thesis is devoted to investigate the extent to which PL information can adequately absolve these two tasks.

Health risk information and specifically package leaflets have been analyzed from different perspectives.

Linguistic analyses have concentrated their focus on the identification of possible sources of uncertainty for the lay reader at different levels of text constitution.

Also research on health risk information seeking behavior and processing has addressed drug information to the patient with a special attention to the uncertainty effect related to health risk disclosure.

These studies implicitly address the core issue concerning PL information: namely the uncertainty affecting health decision making.

In the present perspective, the distinction between residual and avoidable risk allows distinguishing two functions of risk disclosure, namely risk prevention and minimization with respect to avoidable risk, and risk disclosure so as to allow an informed decision with respect to unavoidable (residual) risk.

The explicit distinction between warning (safety protection) and risk disclosure (right to self-determination) calls attention on the decisional aspect entailed in the disclosure of unavoidable risk, therefore opening the way to the identification of a

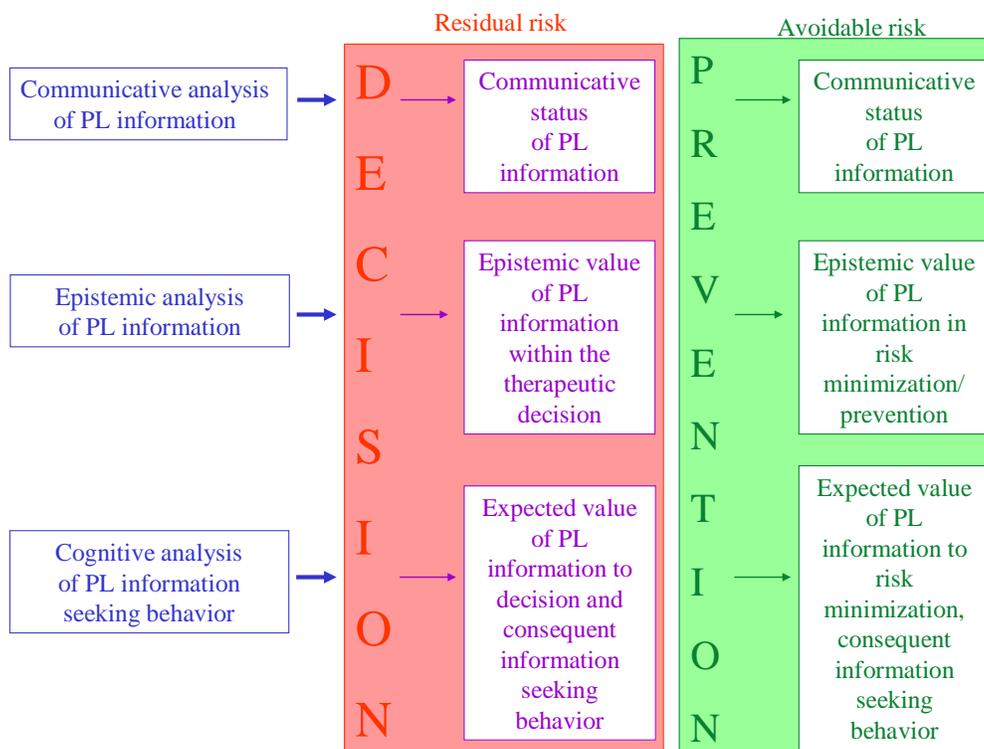
deeper source of uncertainty than that generated by text incomprehensibility, namely the epistemic uncertainty associated to the therapeutic decision.

Thus, the legal analysis of PL information and the consequent identification of the two institutional tasks which it is supposed to accomplish allow clarifying the research question: does PL information constitute an adequate basis for informed consent and therapeutic safety?

Furthermore this question also guides the selection of the most promising methodological tools in relation to the research issue at different levels:

1. The institutional account of PL information allows the identification of its communicative status as a function of the agents involved, related roles and responsibilities. This perspective differentiates the present analysis from previous linguistic research on the topic, which has focused on the textual characteristics of package leaflets, and has failed to clearly distinguish between the two different tasks – safety vs. self-determination information – with a consequent emphasis on the directive force of PL information to the detriment of the more sophisticated communicative nature of risk disclosure for consent.
2. The identification of the self-determination function emphasizes the need for an evaluation of PL information as a basis for decision, in addition to the traditional emphasis on safety. This need results in the search for a methodological tool capable of evaluating the contribution of information within decision: this has been found in Bayesian decision theory.
3. Finally, the analysis of PL information in the perspective offered by decision theory allows providing a unitary account for apparently unrelated phenomena concerning the processing and effect of PL information (information seeking behavior). This is considered as a result of the expected value of PL information to the therapeutic decision and to safety measures during the therapy.

The following scheme presents these three fields of investigation unified by the same underlying perspective: the distinction between the communicative nature of avoidable vs. residual risk information.



**Figure: Work schedule for the analysis of PL information. To the distinction between avoidable and residual risk correspond two different communicative tasks: namely risk prevention (right to safety) and disclosure of residual risk (right to self-determination).**

This chapter presents the state of the art in linguistic research on package leaflets and proposes a speech act definition of their communicative status on the basis of the institutional tasks they are supposed to accomplish.

Chapter 6 will propose an epistemic analysis of PL information: its role in the assessment of a personal risk/benefit prognosis will be analyzed within the framework of Bayesian theory.

Finally, the empirical part of this study will present a series of findings on the processing and the impact of health risk information in general and PL information in particular. The Bayesian theory of the expected value of information *to a decision* provides a key solution to many apparent contrasting phenomena observed in empirical research.

## 2. Linguistic analyses of the package leaflet

The legislator has increasingly ascribed high importance to PL information and has promoted various initiatives aimed at the improvement of PL readability and consumer friendliness.<sup>480</sup>

As a basis for these normative attempts a thorough investigation of the PL text has been undertaken as to the identification of major problems affecting the acquisition and use of PL information. This has generated a number of studies, most of all

<sup>480</sup> See chapter 4 § 4. See also Eckkrammer, 2002: 26 ff. for a comparative perspective.

coming from the linguistic field, which have extensively contributed to the identification of factors at the basis of patient unfriendliness in PL texts.

Analyses range from text typology (Bock 1994; Dontscheva 1990; Ehlich 1994; Ehlich/Noack/Scheiter 1994; Eckkrammer 1995, 1998, 1999, 2002, 2002b; Fickermann 1994; Grosse/Mentrup 1982; Hoffmann et al. 1998, 1999; Langer 1995; Mohn 1991; Nickl 2001; Werner/Heyne 1989) to lexicography (Mentrup 1982, 1988), and pragma-linguistics (Hensel 1989; Hoffmann, 1983; Saile 1984; Schuldt, 1992, 1998, Völzing, 1976, Zacharias, 1986).

Lexicography on one side and “Textsortenlinguistik” on the other, have studied PLs as a special token of text for specialists (“Fachtext”: Mentrup, 1988). The focus of lexicography was to reconstruct specialist lexicons, whereas text typology was concentrated in filtering out convergences and divergences among text types in order to identify constitutional properties of the text as a theoretical construct (Spillner 1981, 1987, 1994, Eckkrammer 2002).

These studies are generally of normative nature, and therefore aim at evaluating PL information quality.

Information quality is addressed through several parameters, such as pharmaceutical reliability, instruction unambiguousness, comprehensibility, and general reader-friendliness.

Recurrent issues dealt within linguistic literature are:

1. Uncertainty induced by *vagueness and ambiguity*.
  - This is ascribed in some instances to “bad news” concealment strategies and product promotion through the lines.
2. Uncertainty induced by *incomprehensibility*.
  - This is principally attributed to specialist language and traces of the PL original use as information for the doctor.
3. Uncertainty induced by *information overload*.
  - This is blamed on the firm’s attempts to possibly avoid liability concerns, but it should be rather ascribed to the legislator’s prescription as for PL information content and design. The regulation in this field is in fact so tight and articulated that very little manoeuvre margins are left to the pharmaceutical firm.

All these phenomena have been analyzed at different discourse levels:

- Text typology (institutional aspect).
- Discourse markers (pragmatic element);
- Grammar (syntactical forms);
- Vocabulary (lexicon);
- Design and layout (graphical-semiotic markers).

In general uncertainty is analyzed in all these studies as an *effect* of PL information on the drug consumer.<sup>481</sup> I will remark at the end of the chapter that however uncertainty is also relative to the *risk inherent to drug use* and that these two sources of uncertainties should be clearly distinguished.

By failing to explicitly discern these two sources of uncertainty, linguistic literature has missed the opportunity to account for the uncertainty inherent to the therapeutic

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<sup>481</sup> “Verunsicherung” in the German literature.

context itself, and to analyze PL information in this respect. This aspect will be dealt with in the next chapter.

## 2.1 Text typology

The typological component is the teleological cause for text configuration and information design. Point of reference of linguistic studies has been the safety aspect of product information, with consequent classification of PL texts as “directive texts”<sup>482</sup>.

The reason for which linguistic analyses have focused on the instructive aspect of PL information and neglected its role within therapeutic consent is to be found in historical/legal factors.

As already mentioned in preceding chapters, the official justification for the introduction of PL has been to protect user safety through adequate product instruction. Also the official label assigned to PLs by the legislator is “Use Information” (“Gebrauchsinformation”). The legislator’s intention to assign PL the additional function of autonomy information has emerged only gradually and has never been officially introduced in the German Medicines Act (AMG).

Hoffmann, for instance, defines three illocutionary points<sup>483</sup> for PL information, none of which considers the special status of information about residual risk (which is not aimed at preventing risk – warning – but merely at notifying it to the reader). In his classification PL content is categorized under the following labels:

1. presentation (of the text itself and of the product – for others also “declaration”<sup>484</sup>).
2. warning;
3. instruction.<sup>485</sup>

The table below divides the different parts of PL content under these three headings:

presentation	warning	instruction
Text type declaration: “Use information”	Side effects	Therapy dosages
product type declaration	Contraindication	Therapy durations
firm	Interference	Countermeasures in case of side effects
components	Security from children access	
components description	Specific warnings	
form of intake	Expiry	

<sup>482</sup> Mentrup, 1982, 9; Eckkrammer, 1995: 188-189.

<sup>483</sup> The terminology comes from speech act theory. Searle and Vanderveken, 1989 distinguish five main categories of speech act along five *illocutionary points*: assertive (e.g. statements); commissive (e.g. promises); directive (e.g. orders); declarative (e.g. declarations); expressive (e.g. congratulations). Different speech acts with the same illocutionary point can be distinguished on their turn through “operations” on the seven components constituting the illocutionary force. For example reporting differs from asserting because of the different propositional condition that the event reported be either in the past or in the present, but not in the future (p. 187); requesting differs from ordering for the position of authority of the speaker (mode of achievement) (p. 201); warning differs from advising for the presupposition (preparatory condition) that the state of affair described by the propositional content is bad for the hearer, whereas in the advice this is good (p. 203).

<sup>484</sup> Möhn, Pelka, 1984: 149, cited in Mentrup, 1988: 195.

<sup>485</sup> Hoffmann, 1983: 141 ff.

**Table 2: Hoffmann’s categorization of PL information content.**

From the legal point of view however, information listed by Hoffmann under “warning”, falls both under safety information (instruction for safe use: in blue) and information about residual risk (side effects: in red). The declaration of side effects is information for consent, given that side effects represent the risk, which the drug consumer should knowledgeably take into account by consenting to the therapy. Therefore this information should not be put in the same category of safety information for preventing avoidable damage.

The merging of different categories of information under the vague label of “warning” can be considered a consequence of the lack of clarity about the two types of risk disclosure (safety instruction and information for consent), whose distinction is entailed by the separation between residual and avoidable risk.

The work of Eckkrammer includes package leaflets as an object of contrastive textual analysis. This approach investigates the nature of PL texts along both pragmatic (“sprachexterne”) parameters such as the editing history, the authors and endorsers of this information, and formal parameters such as information design, syntactical structures and lexicon compared across different cultures or in relation to other text types.<sup>486</sup> The underlying intention is to discover recurrent textual “patterns” associated with specific communicative functions and/or cultures. From a syntactical point of view, for instance, given the modular consumption of PL information, traditional cohesion elements (such as explicit or implicit cross references, causal or consecutive conjunctions, or thema-rhema constructions) are considerably fewer than in other text types.<sup>487</sup>

Eckkrammer defines PLs as a text type with informative-instructive function, subjected to strict legal constraints.<sup>488</sup> Furthermore, she points out the addressee inadequacy to deal with such information: “The patient feels inadequate in many respects; because a real choice presupposes that he has clearly understood what consequences his acting (or non-acting) brings forth”.<sup>489</sup>

Notwithstanding this and other allusions to the decisional aspect of PL information, linguistic analyses have failed to analyze PL texts as a basis for informed consent, and generally define them as “warning” texts.

## **2.2 The communicative status of PL information within the institute of informed consent**

The outline of PL legal nature presented in the preceding chapters allows us to define its communicative status by deriving it from its institutional tasks.

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<sup>486</sup> See Eckkrammer, 2002, 1999, 1998

<sup>487</sup> Eckkrammer, 1999: 91.

<sup>488</sup> Eckkrammer, 2002: 26: “Bei der Packungsbeilage von Medikamenten handelt es sich um eine Textsorte mit informative-instruktiver Funktion, die stringenter rechtlichen Rahmenbedingungen unterliegt”.

<sup>489</sup> Eckkrammer, 1998: 351-352: “der Patient fühlt sich vielfach überfordert, denn eine richtige Entscheidung setzt voraus, dass er genau verstanden hat, welche Konsequenzen sein Handeln (bzw Nicht-Handeln) nach sich zieht”.

As mentioned in the preceding paragraph, package leaflets have been generally categorized as warning texts. However, in classical speech act theory, the act of warning is defined as a subtype of suggestion: to recommend not doing something.<sup>490</sup> This kind of analysis is adequate for that part of risk communication regarding precautionary behavior (the don'ts of the therapy); instead it cannot capture that part of health risk communication addressing the eventuality of damage notwithstanding adherence to precautions, i.e. communication of “residual risk”. *It is precisely by resorting to the technical notion of the word “risk” that the speech act approach gains a deeper insight in the communicative nature of PL information.*

In fact, being adverse drug reactions unavoidably and unpredictably connected to drug intake, the only way to avert them would be to renounce to the therapy. Residual risk information is therefore not aimed to avert damage through precautionary warning, but rather to honor the patient’s right to self-determination, in that he can decide on its basis, whether to undergo the risk or not. Therefore the disclosure of residual risk in the PL counts as a *request for consent*.

This derives from the institutional effects inherent to PL information in the institute of informed consent as it has been illustrated through the preceding chapters.

Furthermore, because of the risk transfer related to consent, the side effects list also counts as a liability *disclaimer*.

How can the simple “act of informing” about side effects validly count as a “request for consent” and “disclaimer”? In order to analyze this issue I will recur to the analysis of communication in institutional settings.

Institutions can be analyzed by examining their fundamental components:<sup>491</sup> a “core ontology” (fragment of social reality regulated by the institution); a set of authorizations (the institutional effects that each member of the institution is empowered to bring about); a set of norms (obligations, rights and permissions assigned to the institution members); finally, a set of conventions associated to the execution of specific institutional effects.

Communication acts among agents in the institution can be defined in terms of institutional effects, i.e. changes which entities may undergo with regard to their status, authority, duties rights, and responsibilities (commitments).

The following chart illustrates the institutional ontology, rules, and conventions concerning the institute of informed consent for drug therapy:

<b>Core ontology</b>	Competent authority (A) Pharmaceutical producer (P) Doctor (D) Drug consumer (C)
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<b>Set of authorizations</b>	1. (A) is authorized to prescribe content and form of product information (§§ 11; 12 28 II nr.2; 29 IIa AMG). 2. (A) is authorized to sanction product circulation with no or not adequate information (§§ 97 II 5 AMG).
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<sup>490</sup> See Searle, Vanderveken: 1989.

<sup>491</sup> Colombetti et al. 2003: 80.

<b>Norms</b>	<ol style="list-style-type: none"> <li>1. (P) is liable for inadequate product instruction (§84 I 1 nr.2 AMG; § 823.1 BGB; § 95: criminal and civil liability)</li> <li>2. (D) is liable for obtaining consent from the patient and to enable his therapeutic decision (§§ 823.1; 280 BGB civil liability: tort and contract)</li> <li>3. The consent is not valid without prior information (for § 2 I GG).</li> <li>4. By consenting to the therapy, (C) thereby shoulders the residual risk entailed by it.</li> </ol>
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<b>Set of conventions</b>	<ol style="list-style-type: none"> <li>1. For (C) with regard to (D): therapy onset upon due information count as <i>consent</i> to the therapy.</li> <li>2. For (C) with regards to (P): drug intake counts as renounce to compensation for residual risk listed in PL (“<i>consent</i> to drug residual risks”).</li> </ol>
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**Table 3: Agents, rules, and conventions of the institution of “pharmaceutical” informed consent.**

In the institute of informed consent for drug therapy, communication is regulated by the authority through prescription norms and liability regulation. These norms make the doctor and the pharmaceutical producer liable for providing adequate information to the patient. Through this information the consent is considered valid, and consequently the responsibility for the residual risk is transferred to the drug consumer: the risks not due to professional errors (negligent prescription or product faultiness) are shouldered by the patient, as stated by the fourth norm.

The simple fact of undertaking the therapy upon due information is considered to count as consent (set of conventions). This is all the more valid for PL information, whose acquisition prior to drug intake is considered as part of the patient’s responsibility.

For the principle of adjacency pair, consent is given to a previous request. Therefore the illocutionary point of the information about side effects is not only “informing” but “making a request”. Indeed it is a request precisely performed by informing. This kind of speech act can be better analyzed by drawing on the concept of declaration in institutional settings.

Institutional contexts make any communicative act (information, request, promise) a declaration.<sup>492</sup> A declaration in standard speech act theory differentiates from other speech acts types by the fact that it is a “performative” sentence: which means, that its content is made true by the very act of uttering it in an appropriate context:<sup>493</sup> “Declaring that an action of type t is performed counts as the actual performance of an action of type t”.<sup>494</sup>

<sup>492</sup> Colombetti et al. 2003: 72, 88-89.

<sup>493</sup> Searles, Vanderveken, 1989: 3.

<sup>494</sup> Colombetti et al. 2003: 88. This is valid for the performance of “institutional acts”. Within standard speech act theory instead, information is not subsumed into the declarative illocutionary force: informing someone that it is raining does not cause to rain. In fact along Searle’s taxonomy, informing is a hearer-directed assertion. Searles, Vanderveken, 1989: 185.

Within an institution, the sharing of information produces at least the institutional effect of *changing the reciprocal status* of sender and receiver with reference to the delivered content.<sup>495</sup>

*The act of informing in an institutional context can be therefore considered a declaration in that it makes true the status of being informed of the receiver.* Once the peace of information has been received, than from that moment on it is manifest (public) that the receiver is informed about it.

For the legal requirements of respect for autonomy, the official status of “being informed” is a sufficient condition for consent to be valid together with therapy onset.

*Correspondingly, information about residual risk is an implicit request for consent, and – given the special provisions related to consent in pharmaceutical setting – it also amounts to a disclaimer: a declarative speech act aiming at a change of informative status in the receiver, with related responsibility reallocation among the parties.*

The analysis of PL institutional effects, allows to determine its communicative statuses (request for consent and disclaimer) and to explain why the general “warning” label only grasps the safety aspect of PL information and fails to describe its role within the institute of informed consent.

### **2.3 Scientific, legal, and linguistic constraints of PL information**

The importance of the institutional environment within which PL information plays its role, has been recently recognized as an essential component of the investigation concerning this text typology.<sup>496</sup> However, it is only in an earlier work of a lexicographer that the linguistic perspective most profitably gains depth of analysis from legal considerations. This is the work of Wolfgang Mentrup. Mentrup’s study originates in that area of research dedicated to the study of “language for special purposes” and translation theory.

Drawing back to Bühler’s “Handlungstheorie” Mentrup describes the parameters relevant to the pragmatic situation (“who”: *Arzt, Doktor, Medikus*; “what”: *Arzneimittel, Analgesikum, Schmerzmittel*; “why”: *Krankheit, Beschwerde, Schmerz*; “to whom”: *Patient, Kranker*) and takes into consideration the institutional and legislative framework (which he calls *meta-text corpus*) in which these texts are

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<sup>495</sup> In fact also Searle and Vanderveken underline this pragmatic aspect of information sharing. While a passive form is possible for verbs such as “put into notice” and “inform”, this is not possible for verbs such as “state” and “assert” (185):

“Thus, for example, one says, “You are hereby notified” or “You are hereby informed”.  
But one cannot, for example say “You are hereby asserted” or you are hereby stated”

The grammatical difference between assert and inform reveals the possibility of an underlying distinction between the act of informing and the act of asserting. This is reflected in institutional contexts; where asserting and informing have different institutional effects. *The first related to the official position held by the speaker on an issue, the second rather to the hearer’s relationship to the information delivered.*

<sup>496</sup> Schuldt, 1992: 41 ff.

embedded. In this sense he is particularly interested in the different degrees of *binding force* expressed by different types of product instruction, where the prescription/prohibition pair is associated with the maximal force.<sup>497</sup>

By combining legal directives with scientific data concerning the product, specific information constraints concerning PLs can be derived. This analysis bears following interesting implications:

- 1) Pharmacological information incorporated in the PL derives its assertive and directive force from the degree of confidence provided by the coherence of statistical data coming from labor experiments, clinical studies, scientific literature etc. For instance, the higher the confidence in the association between the drug intake and the occurrence of a severe side effect for a specific risk group, the more peremptory should be contraindication warnings for this subgroup.<sup>498</sup>
- 2) The binding force of each PL message is a function of the commitment implied by the institutional effect performed by the message.

The following table illustrates the categorization of PL content as a function of the distinction between information for consent and safety information, and of the sub-distinction in prescriptive vs. prohibiting institutional effects.

	<i>Information for consent (assertive)</i>	<i>Safety information (assertive/directive)</i>	
	Request for consent/disclaimer	Prescription	Prohibition
<i>Scientific information supported with different degrees of certainty</i> → (%) (probabilistic data)	Efficacy Residual risk (side effects)	Dosage Duration Preservation	Contraindications Interference Precautions

**Table 4: Scientific, legal, and linguistic constraints of PL information**

Information for consent is given in assertive form, even though it bears the illocutionary point of a request. Safety information is provided in both assertive and directive form, but it fundamentally bears directive illocutionary points such as ‘prohibition’ or ‘warning’ and ‘prescription’ or ‘recommendation’. The binding force of all indications depends on the scientific evidence supporting the data, which is determined in probabilistic terms.

*Along this table, PL text type can be defined as a filtered source of probabilistic information for the lay user, declined in directive instructions for safe use, and in assertive information about risk and benefit data bearing the illocutionary points of ‘request for consent’ and ‘disclaimer’ at the same time.*

<sup>497</sup> Mentrup, 1988: 184.

<sup>498</sup> See chapter 6.

## 2.4 Pragmasemantics of package leaflets

On the benchmark provided by table 2, it is possible to explain some sources of uncertainty identified at different textual levels.

The highest level of uncertainty is represented by pragmatic ambiguity and vagueness. Ambiguity originates for instance when instructions are delivered in assertive forms through presuppositions or implications rather than explicitly in directive form, or when, instead of clearly prohibiting or prescribing a specific behavior, the text leaves open more than one alternative.<sup>499</sup>

The phenomenon of pragmatic ambiguousness is also exemplified by polite recommendations substituting strict prohibition, and therefore letting the reader uncertain as the nature of the directive instruction (permission with reserve or respectful prohibition?).<sup>500</sup>

Hoffmann qualifies these phenomena as “Entwarnung” (“dis-warning”), i.e. toning down of warnings through ambiguous speech acts (“*des Offenhaltens*”).<sup>501</sup>

This kind of ambiguity is also represented by the weakening of the directive peremptoriness through concessive sentences: an arbitrary space for deviance from the forbidden/prescribed act is opened, which the lay reader does not know how to make use of. This is also valid for sentences, followed by an adversative which partly contradict, or specifies their content.<sup>502</sup> The effort required for bringing these contradictions to coherence, is often perceived as unsuccessful/unworthy and eventually leads to increased uncertainty (for instance as to drug risk estimation or as to the right behavior to undertake).

To the pragmatic ambiguity of assertive sentences implicating an instruction a source of semantic vagueness is added in sentences like “X and Y can influence each other”: not only it is left unclear what conclusions the reader should draw from the message. More fundamentally, the verb ‘influence’ leaves unclear whether the sentence should be interpreted as a warning about *toxicity/effectiveness increase* of x through y, and vice-versa or as a *toxicity/effectiveness decrease*.<sup>503</sup>

Pander Maat explains the lack of explicitness of many PL text passages as a consequence of the author’s reliance on the reader’s inferential work.<sup>504</sup> However, this is precisely the core problem of expert-to-lay communication. The expert might not appropriately calibrate his discourse to the lay level of inferential capacity, which in the case of PLs, is severely compromised by pharmacological and medical incompetence. This is all the truer, when considering mass media texts,<sup>505</sup> directed at a heterogeneous audience consisting of readers with different degrees of health

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<sup>499</sup> Schuldt, 1992: 185 ff; 205: “Die Einschränkung des Warnhinweises durch die Verwendung mit konzessiven Konjunktionen oder Adverbien eingeleiteten Nebensätzen stellt eine Verunsicherung des Arzneimittelverbraucher dar”.

<sup>500</sup> Zacharias, 1986: 94 f.; Schuldt, 1992: 201 ff; 216 ff. also with improvement proposals: “«Bei Y *muss* das Präparat *sofort abgesetzt* werden» statt als «Bei Y *sollte* das Präparat *nicht mehr angewendet* werden »” (249). With a different pragmatic interpretation, Pander Maat, 1997: 118 ff, 124.

<sup>501</sup> Hoffmann, 1983: 150 ff.

<sup>502</sup> See Zacharias, 1986: 41 ff.

<sup>503</sup> Zacharias, 1986: 92.

<sup>504</sup> Pander Maat, 1997: 124.

<sup>505</sup> Pander Maat, 1997: 112.

literacy and processing capacity. Also in case of procedural knowledge – for instance what to do in case of side effects – Pander Maat attributes the low presence of instruction as the result of the author’s assumption that one should not consult the doctor, unless advised to do so!<sup>506</sup> By limiting his analysis equipment to pragmatic-linguistic instruments (cooperation principle, conversational maxims, implicatures) Pander Maat fails to identify the institutional origin of many textual formulae. However he succeeds in bringing to light the consequences which these formulae have on the reader’s side.<sup>507</sup>

Another source of uncertainty at the pragmatic level is constituted by the multiple addressing. Sentences such as “if the doctor did not prescribe other dosage” are followed by sentences such as: “patients with tendency to X should not be prescribed this treatment”. The information target is ambiguous and oscillates between doctor and patient. The unsteady alternation of passages directed at the doctor with passages directed at the patient is considered all the more reproachable, as this is done without explicit markers.<sup>508</sup>

Sometimes the text assumes the tone of “exclusive insider conversation” where the doctor is also addressed as an interested addressee of research results.<sup>509</sup>

Several contributions criticize the exploitation of an instructive text for marketing purposes (Hoffmann 1983; Zacharias 1986). Indeed, many studies explore PLs as an occasion for the firm to increment user fidelity and image reputation in general (Arnold et. Al. 1984; Bönsch, 1986; Gebert 1988; Naether 1984; Petersen et al. 1985). The critiques moved at these marketing attempts are based on the consideration, that PL information cannot be “contaminated” through other communicative functions other than the institutional official purpose of use safety. A “purist” view which is also confirmed by the legislator through § 11 AMG, where it is prescribed to clearly separate additional information spontaneously provided by the pharmaceutical firm, from the official information strictly prescribed in § 11, nr. 1-8.

#### 2.4.1 Semantic analysis of frequency descriptors

From the point of view of information for consent, the major uncertainty is constituted by the probabilistic form of this information. Probability is inherent to the concept of risk, and pharmaceutical risk is no exception.<sup>510</sup> A probabilistic assertion such as:

“(On the basis of available pharmacological data) the occurrence of side effect x can be estimated as  $10^{-6}$ ”

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<sup>506</sup> Pander Maat, 1997: 125.

<sup>507</sup> See for instance Pander Maat, 1997: 125-126, 127 ff.

<sup>508</sup> Zacharias, 1986: 54: “Sollten in Einzelfällen stärkere Beschwerden auftreten, so ist dies dem Arzt mitzuteilen ... Patienten, die (XYZ) hatten, sollten beobachtet werden”.

<sup>509</sup> Zacharias, 1986: 58.

<sup>510</sup> Throughout this work, I have adopted the legal notion of pharmaceutical risk as health injury. The probabilistic dimension is considered in this context as an additional attribute, rather than the risk itself. As for the polisemy of this term within risk theories see Preuss, S.: 1996: 68.

entails a commitment to the truth of the probabilistic assertion.<sup>511</sup> This sentence simply refers to the proportion of cases in which side effects x occurred out of the entire population who took the drug. In probabilistic terms, this means that on the basis of the available knowledge the hypothesis that side effect x occurs is supported by the data to  $10^{-6}$  degree of confidence.

However, in order for this information to be of any use for the reader, the probabilistic assertion should be translated in a prognostic assessment about the *personal probability* that he might be concerned by the side effect mentioned.

The translation of frequency data into personal probability estimations is a hot topic within probability theory, which leads to questions of the type: Is it legitimate to derive a personal estimation from general frequency data? If yes, is it feasible? If not, what is the value of frequency information in PLs? Can this information be considered of any use for giving a rational consent?<sup>512</sup> This issue will be extensively considered in the next chapter. Here a study comparing the interpretation of verbal and numeric frequency quantifiers is presented, which sheds some light on the meaning attributed to probabilistic information by lay readers. From the study, conducted by Pander Maat and Klaassen (1994) it seems in fact that quantifiers are rather used in the phase of information processing as a filter for selecting side effects on the basis of their occurrence probability. Instead, in a second time, only selected side effects are remembered with no associated frequency. Frequency descriptor themselves are not memorized.<sup>513</sup>

This could be illustrated by recurring to the analogy of a “signal detector” system. In this model a specific frequency descriptor – for instance “uncommon”) – is assigned the minimal level of detection for deciding whether to store a signal or not. Beyond this level, no signal is deemed worth of consideration, and therefore all side effects associated with frequencies below the threshold level are completely neglected by the system.

<sup>511</sup> This is different from a probabilistic commitment to degree  $10^{-6}$  that the assertion is true. See also Carnap: 1962: 30.

<sup>512</sup> I will address these issues in the next chapters by drawing on categories and instruments devised by probability and decision theory.

<sup>513</sup> It also emerges a tendency to assign verbal quantifiers – such as “sometimes”, “seldom”, “very seldom” – a considerably higher frequency in relation to their standard meanings. This is a very interesting datum in the context of expert-to-lay communication analysis. The standardization determined by policy requirements may be extraneous to the lay reader and therefore lead to misunderstandings.

These have been recently harmonized by the European agency EMEA through the Summary of Product Characteristics Guideline: <http://www.bfarm.de/de/Arzneimittel/index.php?more=SPCGuideline-Bekanntm2.php>. Below the German version implemented by the Bundesinstitut für Arzneimittel und Medizinprodukte: BfArM):

SPC-Guideline	German	%-indication
Very common	sehr häufig	$\geq 10\%$
common	häufig	$\geq 1\% - < 10\%$
uncommon	gelegentlich	$\geq 0,1\% - < 1\%$
rare	selten	$\geq 0,01\% - < 0,1\%$
very rare	sehr selten	$< 0,01\%$ **

\*\* single cases are listed under this category.

Side Effects	Frequency descriptors	Memory threshold	Output
SE <sub>1a</sub> SE <sub>2a</sub> SE <sub>3a</sub> SE <sub>4a</sub>	Very common	←	Remembered SE ( <b>without</b> associated frequency): SE <sub>1a</sub> - SE <sub>4c</sub>
SE <sub>1b</sub> SE <sub>2b</sub> SE <sub>3b</sub> SE <sub>4b</sub>	Common		
SE <sub>1c</sub> SE <sub>2c</sub> SE <sub>3c</sub> SE <sub>4c</sub>	Uncommon		
SE <sub>1d</sub> SE <sub>2d</sub> SE <sub>3d</sub> SE <sub>4d</sub>	Seldom		Deleted SE: SE <sub>1d</sub> - SE <sub>4e</sub>
SE <sub>1e</sub> SE <sub>2e</sub> SE <sub>3e</sub> SE <sub>4e</sub>	Very seldom		

In this experimental study, the frequency associated to side effects only indirectly contributed to the did evaluation of drug toxicity. The authors conclude “that individual differences in FD [Frequency descriptors] interpretations do not systematically affect drug evaluations, recall of side effects and reporting rates of side effects”.<sup>514</sup>

Pander Maat explains this datum with reference to the risk acceptance level. He adduces that: “Considering the fact that SEs are the logical consequence of a behavior (using a drug) that one is more or less willfully engaged in, it seems reasonable to assume that what someone considers to be a normal frequency, will often be the *acceptable* frequency: i.e. the risk that is taken into the bargain. Therefore, individual differences between frequency expectations do not necessary result in different evaluations of the drug”.<sup>515</sup>

It could also be assumed that this phenomenon speaks for a “0 or 1” attitude towards SE information. The drug consumer considers that either will he be concerned by the SE or not. It makes no difference to his prognosis whether, on a general level, a SE concerns 1 out of 1000, or 1 out of 1000.000 users. Therefore, either he decides to undergo the risk of being concerned by the side effect or not. Whenever he has decided to accept the side effects listed in the PL, their general frequency of occurrence does not change his evaluation of the personal danger he is exposed to.

It seems therefore that uncertainty generated by probabilistic data might be coped with by ignoring it, i.e. either by setting the risk at 1 or at 0.

The way the lay reader deal with probabilistic information is a central issue in the investigation of PL role in therapy decision. This will be the major topic of the experimental part of this work. As for the study conducted by Pander Maat and Klaassen, linguistic considerations need to be pointed out, before their findings can be generalized. In fact semantic aspects related to textual interpretation might act as a confounding factor in the study of the interpretation of frequency quantifiers.

This is because in normal contexts, the quantifier acts as a quasi-focus in the message but it is not itself on focus.<sup>516</sup> The consequence is that in the context of PL, the quantifier “seldom” is not considered as an autonomous peace of information, but just a complement to the side-effect to which it is associated: “Nervous disturbs

<sup>514</sup> Pander Maat, Klaassen, 1994: 401.

<sup>515</sup> Pander Maat, 1997: 134.

<sup>516</sup> See Rigotti, 1993: 87 for a semantic distinction of sentences with quantifiers as cataforic elements with a rhematic function or as fully rhematic elements.

seldom occur<sup>517</sup>. In this format, the message could be pragmatically read as an instruction to consider the side-effect as negligible.<sup>517</sup>

In order to proof that frequency descriptors function analogously to detection signals, one should put the sentence in a form where both the side effect and the frequency are in focus:

*Side effects*

Head-ache: seldom;

Stomach-ache: uncommon

.....

Or even better in a tabular form:

SE \ frequency	Very common	common	uncommon	seldom	Very seldom
Head-ache		x			
Stomach-ache	x				
....					x
....				x	

However, more and more PLs are adopting exactly this display format, and also the numerical version of frequency indication (or at least both verbal and statistical information) has been introduced in most PLs. These forms of information design neutralize the thema-rhema construction and therefore constitute the most suitable form to communicate frequencies.

## 2.5 Lexicon

The most investigated characteristic of PL texts is the uncertainty generated by medical, pharmacological, chemical and technical vocabulary in general.<sup>518</sup>

The old PLs contemporarily and ambiguously addressed a multiple and heterogeneous audience (both the medical professional and the lay reader). Even where separate leaflets have been adopted for doctor and patient, many traces of this phenomenon are to be found in the texts. This factor is identified as one major source of scarce readability (Beimel 1986; Bürkle 1984; Gloning 1995; Hoffmann, 1983; Krautmann, 1981; Lehl et al., 1982; Noack 1991; Schuldt, 1992; Zacharias, 1986).

Before and soon after the introduction of separate information for doctor and patient, many efforts have been devoted to the identification of formulations and words, which could be felt as unfamiliar by the lay reader and therefore skipped over because considered to be addressed to the expert (the doctor).

This phenomenon is not limited to technical words, but also to instructions which presuppose expert knowledge.

Specialized lexicon is categorized in strictly technical terminology – only comprehensible to the insider – and specialized language which has entered to a greater or minor extent in the common use. Both constitute a source of

<sup>517</sup> See also Zacharias, 1986: 61, 89 for critical analysis of such formulae.

<sup>518</sup> Hoffmann, 1983: 143 ff.

misinterpretations and cognitive uncertainty. In the first case text understanding is completely blocked, therefore creating “interpretation holes”. In the second case, the ordinary use of a specialized term might more often than not differ from its technical meaning and therefore generate misunderstandings.<sup>519</sup>

Thanks to considerable efforts, PL vocabulary has significantly improved towards comprehensibility and reader-friendliness. Most of technical words have now been substituted by more familiar terms.<sup>520</sup>

## 2.6 Design and layout

A major fault in PLs has been found in a homogeneous text design devoid of textual cues and markers for a hierarchical organization of the information to be acquired. Also this aspect is due to legal constraints. In fact such an organization of the data would imply that some pieces of information are more relevant than others, while this is incorrect from a legal perspective, according to which all information delivered in the PL is equally important.<sup>521</sup> The European Readability Guideline (see § 2) has brought a major change to this aspect of readability.<sup>522</sup> Still, font dimension and the repetition of same blocks of information under different subsections are critical points, which require further efforts of improvement.

## 2.7 Information overload

Anxiety induction through warnings lists and consequent hindering of compliance has been generally attributed to information overload (Aumiller, 1978, 1982; Degner, 1982, Karpa, 1991, Kepplinger 1990, 1991, Nickolaus, 1991; Nöthlich, 1991; Wenzel, 1985; Winkelmann, 1983; Wolff, 1982; Zink, 1985; Zylka, 1986)<sup>523</sup>. Referring to the long lists of warnings Eckkrammer (2002) coins the expression: “liability offload”.<sup>524</sup>

However, also for the concept of “information overload”, it should be distinguished between a cognitive overload, which is the perception resulting in general from *difficult* texts and an overload of risk information, which is objectively *frightening* for the reader.

Cognitive overload is a relational parameter which depends on personal relevance, content type and cognitive costs required for elaborating information. The relationship can be roughly formulized as follows:

$$CO = C/R \cdot T (-\infty; +\infty)$$

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<sup>519</sup> Hoffmann, 1983: 143; Schuldt, 1992: 167-184; Mentrup, 117 ff., 155 f.

<sup>520</sup> For instance, Latin words have totally disappeared. See Eckkrammer, 1999: 100 ff.

<sup>521</sup> Mentrup, 1988: 372, also cited in Schuldt, 1992: 161.

<sup>522</sup> See § 2.7 in this chapter.

<sup>523</sup> I mention here also Askehave et al. (2003) dedicated to graphical aspects of text design.

<sup>524</sup> See also Mentrup, 1988: 314 ff.

(Where CO stays for cognitive overload; C for cognitive costs; R for relevance; and T for topic: the  $-\infty$ ;  $+\infty$  signs stay for a continuous function representing the positive/negative involvement in the topic).

For instance, a novel, which is in general much longer than a normal PL does not give rise to the sense of information overload experienced by PL reader, even if it contains many more data to be elaborated. This is due to the quotient of pleasure represented by its content type.

The sensation of cognitive overload is in general directly proportional to parameters such as topic involvement and inversely proportional to difficulty – and topic aversion.<sup>525</sup>

Health risk information is generally categorized as anxiety inducing information (“bad news”), a fact which, it is highly relevant and unwelcome at the same time.

This contributes to explain the *schizophrenic attitude towards this sort of information*.

In fact, for a lay reader, all listed side effects can be virtually relevant: however he will be precisely preoccupied to assess that the least possible information concerns him. Yet, given his incompetence he will not be able to assess which risks might concern him and which not, eventually falling into a “prognostic paralysis”.

Chapter 9 will deal with these aspects of health risk learning in detail by explaining attitude towards risk information as a function of the parameters determining the decision at stake (availability of alternatives, perceived control over the risk a.o.).

### 3. European readability guidelines

The insights in PL information processing derived from linguistic studies have received increased attention by the legislator, and finally found the most mature implementation in the European guideline issued in 1998 by the European Council: [“A Guideline on the readability of the Label and Package Leaflet of Medicinal Products for Human Use”](#).

The document has been officially implemented in the German legislation in 2002, through the recommendations for the configuration of package leaflet, and translated in legal norms through the 14<sup>th</sup> amendment to AMG.<sup>526</sup>

Several advices provide valuable indications as for the graphics, the design and preferred syntactic structures; also fixed formulas and criteria for listing side-effects or contraindications are included. As for color, it can be used for titles, but red is reserved to very special warnings.

Attention is paid not only to readability in terms of declarative knowledge, but also to explicitness and clarity of procedural instructions: “A precaution should be presented as implying the action a patient should take, rather than as factual information which describes a medical condition” (p.19 Annex 1b); “Explanations should be placed immediately after the instructions when: an instruction is contrary to expected behavior, the reasons for an instruction are not self evident, an

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<sup>525</sup> The estimation of text length is a function of the perceived difficulty: Bartke, 1987: 33, cited in Schuldt, 1992: 208.

<sup>526</sup> See chapter 4 § 4.2

instruction can be made more memorable by using an explanation” (p. 21 Annex 1b).<sup>527</sup> Furthermore, the appendix presents guidelines for readability tests, which the pharmaceutical firm can carry out on their own.

The improvement of these legal initiatives on PL readability is considerable. Both general readability and local comprehensibility of PL texts are by far greater than for PL texts of the preceding eras. However, as recent studies demonstrate, this textual improvement has not been accompanied by an equal decrease of uncertainty<sup>528</sup> or increase in compliance.<sup>529</sup>

It might be therefore worth investigate, whether uncertainty induced by PLs is merely of cognitive nature, or if it is rather linked to more structural questions such as the consideration of the unavoidable risk represented by side effects.

#### **4. Irreducible uncertainty: pharmaceutical residual risk**

In the studies presented above, somehow contradictory charges are moved against PL information. On one side, PLs are blamed of toning down risk information, on the other side they are accused of hindering compliance through long lists of side effects and threatening medical information. Their specialist language is often held responsible for incomprehensibility and consequent uncertainty effects in the reader, but their medical impreciseness is considered as a source of unsafe use.

It seems that PL information indeed is a mixture of such reassuring and threatening messages. However, information design cannot be held the only responsible for these contradictory effects.

For instance, comprehensibility is not the solution to compliance fostering, if one considers that the uncertainty generated by a medical expression, can be even augmented if translated in common language, when it discloses a fatal risk: “Heart block” is certainly no more reassuring than “Atrioventricular-Block”.<sup>530</sup>

Therefore it should be distinguished between a cognitive uncertainty generated by the insecurity of lay reader to assign definite meanings to medical words, or to interpret vague instructions, and a prognostic uncertainty about the (short, medium, long term) risks mentioned in the PL. This is precisely the uncertainty affecting any decision under imperfect knowledge.

The linguistic approach has for obvious reasons studied those aspects of PL information, which can be improved through better communication.

However, the irreducible uncertainty generated by residual risk constitutes an insurmountable barrier to the improvement of patient-friendliness through

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<sup>527</sup> These harmonization directives follow two decisions about authorization for market approval: [art. 14 75/319/CEE](#) and [art. 22 81/851/CEE](#) as well as directives concerning consumer information (dangerous substances, fraudulent and comparative advertising: <http://europa.eu.int/scadplus/leg/it/s16400.htm>). The first European directive on pharmaceuticals was issued in 1965: [65/65/EEC](#).

<sup>528</sup> Nink, Schroeder, 2006.

<sup>529</sup> Bronder, Klimpel: 2001. See chapter 4 § 4.3.

<sup>530</sup> Schuldt, 1992: 176.

communication techniques. No matter how readable, comprehensible and well designed, no PL could promise a risk-free therapy.<sup>531</sup>

In order to analyze the extent to which PL information accomplishes its institutional tasks, attention should be paid to its *epistemic* contribution in providing the knowledge required for consent to be informed and for therapy to be safe.

## 5. Summary and conclusion

This chapter has been devoted to the communicative analysis of PL texts. A definition of the communicative status of PL information has been proposed, on the basis of its institutional tasks. Drawing on categories borrowed from speech act theory, and considering its role within the institution of “informed consent”, a double illocutionary point, in parallel to its double legal effect has been identified for PL information: *request for consent and disclaimer* about the residual risk connected to the therapy.

From a text-typological perspective, PL texts have been defined as a filtered source of probabilistic information for the lay user, declined in directive instructions for safe use, and in assertive information about risk and benefit data, bearing the illocutionary points of ‘request for consent’ and ‘disclaimer’ at the same time.

After presenting an overview of major linguistic sources of uncertainty identified by lexical, linguistic, and textological literature, an inevitable source of uncertainty has been identified, this is related to the therapeutic decision itself.

This insight requires a methodological turn and calls for the analysis of PL information within the framework of decision theory.

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<sup>531</sup> „Trotz aller Bemühungen, die Patienteninformationen besser verständlich zu machen, darf nicht übersehen werden, dass die *Patientenfreundlichkeit dieser Texte ihre Grenzen hat*. Sie haben den unterschiedlichen Vorstellungen der Beteiligten zu genügen. *Haftungsfragen spielen eine Rolle*; Verbraucher haben den berechtigten Anspruch auf umfassende Information, gleichzeitig wird aber die Fülle der Angaben, insbesondere der als abschreckend empfundenen Risikoangaben, beklagt. Dieses Dilemma wird kaum aufzulösen sein, und vermutlich wird die Diskussion um verbraucherfreundliche Packungsbeilagen nie ganz verstummen“: Schraitle, 2006: 4 (my emphasis).



## 6 Bayesian analysis of PL information

*"No one feels strongly about things he takes for granted"*  
Frank P. Ramsey, Truth and probability, 1926.

*"Socrates argues (Symposium, 200) that Love is not a god because to desire something is to be in want of it: you cannot desire what you already have... Thus, to vary the example of the 'Symposium' since people do not always know when they are loved, it is entirely possible to desire someone's love when you already have it. Therefore, it seems better to say that you cannot desire what you think you have".*

Richard C. Jeffrey, The logic of decision, 1990 (1965).

### 1. PL information as a basis for informed consent

Drug information contained in the Summary of Product Characteristics – from which PL information is derived – comprehends data concerning the pharmacokinetics (absorption, distribution, metabolism, excretion), pharmacodynamics (receptors, ion channels, enzymes, immune system), pharmacoepidemiology and –toxicology (the statistical investigation of the drug impact over a population of interest) of the molecular entity(ies) which compound the drug.

Therapeutic indication, efficacy range, interference with other drugs, chemical entities or food in general, contraindications and precautions with regards to specific risk groups and adverse drug reactions (side effects) observed in the pre-marketing phase are also reported in the SPC (and in the PL) and continuously updated in the post-marketing phase through pharmacosurveillance.<sup>532</sup>

These data belong to the documentation required for drug approval, and they are fundamentally aimed at providing the basis for a risk/benefit assessment of the candidate molecular entity; i.e. they should provide the basis for an *informed policy decision*.<sup>533</sup> The administrative authority is supposed to substantiate and legitimize his decision through reference to the amount of expected benefit and expected risk on the relevant population (normally coincident with the group of potential drug consumers, i.e those diseased people, whose condition is expected to be favorably affected by the drug).

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<sup>532</sup> See chapter 4 § 4.1.

<sup>533</sup> See chapter 1.

As already seen in the first chapter, this decision is all but obvious and must take into account several parameters, not only purely pharmaceutical-medical, but also psycho-sociological and economical.<sup>534</sup>

The duty to accompany pharmaceutical products with a package leaflet for the end-user originated within safety regulation with the explicit purpose of fostering use safety and efficacy.<sup>535</sup>

Instead, the legislator does not explicitly refer to PL information as a source for the consumer's decision. Nevertheless, the teleological interpretation of liability norms within drug regulation, (disclaiming function from residual risk, information for consent) and court judgments qualify the PL as a source of information for therapeutic consent.<sup>536</sup>

Therefore the normative analysis of PL information as a legally binding tool should examine to what extent, PL information meets the desiderata entailed by the tasks it is supposed to accomplish: i.e. whether PL information enables a safe use, and whether consent based on PL information is really informed.

This chapter will focus on the second issue and investigate PL information with respect to its role within informed consent by answering the following questions:<sup>537</sup>

1. What requirements the legislator establishes for consent to be qualified as informed;
2. Whether PL information fulfils these requirements.

## 1.1 A Bayesian legislator

The legal doctrine of informed consent has not yet explicitly produced a definition of what qualifies consent as informed. The institute has originated with the recognition of the patient's right to self-determination and autonomous decision, and it has evolved through case law by specifying the conditions which define a choice as autonomous and free. The development of disclosure standards has gone hand-in-hand with a deeper understanding of the factors determining choice.<sup>538</sup> In general

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<sup>534</sup> See chapter 1 § 3.3.4 (risk acceptance).

<sup>535</sup> See Chapter 1 § 2.2. I represent here § 1 AMG for the reader's convenience: „Es ist der Zweck dieses Gesetzes, im Interesse einer ordnungsgemäßen Arzneimittelversorgung von Mensch und Tier für die Sicherheit im Verkehr mit Arzneimitteln, insbesondere für die Qualität, Wirksamkeit und Unbedenklichkeit der Arzneimittel nach Maßgabe der folgenden Vorschriften zu sorgen“.

<sup>536</sup> See chapter 4, especially the sentence LG Dortmund 6. 10. 1999, MedR 2000.

<sup>537</sup> The emphasis on the self-determination function rather than on the safety function of PL information is precisely due to the legal debate around this aspect of drug information as problematized in the literature and in recent court judgments. However, at the end of the chapter also the epistemic contribution of PL information to therapeutic safety will be briefly discussed.

<sup>538</sup> „Die Rechtsprechung [tendiert] zu einer ständigen Ausdehnung der ärztlichen Aufklärungspflicht, um angesichts der sich vervielfältigenden Möglichkeiten der modernen Medizin das Selbstbestimmungsrecht des Patienten zu behaupten“: Emmerich, 2006: 846. See chapter 3 § 5. This is especially valid for the U.S. regulation: see Faden et al. (1986). For a comparison between the German and the U.S. institute of informed consent see Glatz (1998).

court decisions imply that the patient is made aware of the nature of the intervention, its risks and benefits, and the probability thereof.<sup>539</sup>

Essentially, the principle of proportionality determines the amount and level of information detail in relation to:

1. the therapy risk;
2. illness severity (inverse proportionality);
3. the benefit magnitude and probability.<sup>540</sup>

The notion of risk in this setting equates to the magnitude of the expected damage multiplied by the probability of its occurrence. The same is valid for the expected benefit: both beneficial and damaging consequences of the choices are weighted by the probability of their occurrence.

The criterion of including probabilities as relevant information for choice mirrors the procedure developed in the framework of probabilistic decision making: Bayesian decision theory.<sup>541</sup>

The Bayesian approach to informed consent seems to underlie also the regulation of PL risk disclosure, as can be evinced from article 13.1 of the 1994 BfArM recommendations for PL information, which suggests *giving frequency of side effects whenever possible, in order to ease the risk estimation of the patient.*<sup>542</sup>

Thus, PL information is precisely thought of by the legislator as a source of probabilistic information for an autonomous decision, with related shouldering of residual risk.

The point is however whether this information source can indeed accomplish the tasks imposed on it by the legislator.

In order to answer this question these steps will be followed:

1. a Bayesian model of health decision-making will be presented and used as a basis for defining the conditions for consent to be informed;
2. the extent to which PL information can contribute to consent will be investigated on the benchmark of this model.

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<sup>539</sup> BGH NJW 1980, 847; NJW 1982, 147; NJW 1985, 2192; NJW 1989, 1533; OLG Köln VersR 1997, 1491.

<sup>540</sup> The higher the risk, the greater is the detail and quantity of information which should support the decision. The risk disclosure duty also depends from the illness severity: the less severe is the illness the more detailed must be the information about the intervention and related risks. See: Krudop-Scholz, 2005: 97. Also the expected benefit determines the disclosure duty standards: The less important is the expected benefit, the more detailed has to be any information about the risks. Wagner, 2004: 1839 Rn. 705; with reference to BGH NJW, 1991, 2342, and OLG München VersR, 1988, 525 f. Moreover the magnitude of the risk should be gauged not only in abstract terms but also in relation to the specific individual. Any risks must be disclosed whose realization can represent a severe compromise of life quality and/or professional capability for the individual. BGH, NJW 2000, 1784 (1785). See also Krudop-Scholz, 2005: 96-97; 134. Francke, Hart, 1999: 57. (chapter 3 § 5.3).

<sup>541</sup> With the caveat that in the frame of informed consent – at least within the tort liability setting – the decision is understood as a yes/no option rather than a choice among several alternatives. The decision-maker needs to be made aware of the risks and benefits of the proposed intervention mainly. A duty to inform about alternatives is triggered only insofar they are attached with a significantly different risk/benefit profile. See chapter 3 § 4.

<sup>542</sup> See original excerpt in chapter 4 § 4.2, footnote: 35.

## 1.2 Elements of Bayesian decision theory

Bayesian theory models the choice among different alternatives as the selection of the act which brings the highest outcome sum, where each outcome is weighted by the probability of the related state of an affair: this is said to be the act which maximizes the subjective expected utility. “Expected” refers to the probability distribution over the possible outcomes that the act could bring, “subjective” to the fact that this probability distribution results from the decision maker’s knowledge of the state of affairs at the time of decision.<sup>543</sup> The maximization formula reads as follows:

$$(1) \max \{ \sum_{i=1} P(S_i)U(a_j) \}.$$

An example may help illustrate the principle. Listening to the weather forecast on different channels, and relying on the sky at sunset, an agent planning his week-end judges the probability of rain rather low (1/3 of the probability of variable weather). Sunny weather should be twice as probable as variable weather. Therefore the probability distribution about the agent’s weather forecast would look like the following: sunny weather: .6; unsettled weather: .3; rain: .1.

The probability distribution applied to the possible weather conditions for the decision gives the following matrix:

	 S <sub>1</sub> .6	 S <sub>2</sub> .3	 S <sub>3</sub> .1
a <sub>1</sub> picnic	Outcome <sub>11</sub> <b>100</b>	Outcome <sub>12</sub> 0	Outcome <sub>13</sub> -100
a <sub>2</sub> big-town-sightseeing	Outcome <sub>21</sub> 0	Outcome <sub>22</sub> <b>70</b>	Outcome <sub>23</sub> - 20
a <sub>3</sub> museum	Outcome <sub>31</sub> - 100	Outcome <sub>32</sub> 0	Outcome <sub>33</sub> <b>80</b>

<sup>543</sup> Indeed, the emergence of decision theory is intrinsically intertwined with the evolution of subjective probability theory. Whereas first mathematicians and philosophers of science and then logicians have developed a probability calculus, economists and philosophers of mathematics (Frank Ramsey, Leonard Savage, Harold Jeffreys, Rudolf Carnap, Richard Jeffrey, to mention but a few) have developed a theory of rational decision and action on the basis of probabilistic knowledge: Bayesian theory. The connection between probability and decision has been modeled by Neumann and von Morgenstern (von Neumann, Morgenstern, 1944). The integration of the probability calculus into the Bayesian theory of belief has been carried out by Frank Ramsey in his intent to demonstrate the epistemic reality of probability as a measure of the degree of belief upon which one is ready to act. In his account, probability is not functional to decision, but rather the contrary: decisional behavior is the observable effect of the extent to which specific beliefs are entertained by the agent (Ramsey, 1931: 173 ff). This assumption is formalized in Jeffrey’s system, in that the probability is identified with the readiness to act on the basis of a belief and its welcomeness: the technical term used by Jeffrey is: “desirability”. See for instance Jeffrey, 1965, 1968. Savage develops the “subjective utility principle” for maximizing decision, by applying Ramsey’s subjective probability system to von Neumann and Morgenstern model (Savage, 1954).

The expected utility formula gives following results for each act under consideration:

$$\begin{aligned} \text{SEU}(a_1): \sum P(S)U(a_1) &= 100(.6) + 0(.3) + (-100)(.1) = 50 \leftarrow \max \\ \text{SEU}(a_2): \sum P(S)U(a_1) &= 0(.6) + 70(.3) + (-20)(.1) = 19 \\ \text{SEU}(a_3): \sum P(S)U(a_1) &= -100(.6) + 0(.3) + (80)(.1) = -52 \end{aligned}$$

The maximum result is 50: the principle of expected utility maximization prescribes to choose act  $a_1$ : going out for a picnic.

Of course different weather forecasts would lead to different results. Therefore further information can eventually lead to a decision change. The expected value of further information to the decision will depend on its expected epistemic impact on the probability distribution related to the relevant states.

Indeed Bayesian theory results from the development of three distinct but interconnected fields of research devised in order to describe (and optimize) the management of decisions under uncertainty:

- 4) the theory of *decision optimization* through maximization of the expected utility;
- 5) the theory of *knowledge updating* through probabilistic induction;
- 6) the theory of *expected value of information* as a function of the expected reward in terms of contribution to decision optimization.

“Uncertainty” means in this framework an epistemic state of less than perfect knowledge about the actual state of affairs, which is modeled by a probability distribution/function over a state partition.<sup>544</sup>

Bayesian theory therefore allows investigating PL information:

- as a support for decision optimization based on the expected reward of taking the drug vs. not taking it;
- as a basis for knowledge updating (magnitude and probability of side effects occurrence) for a risk/benefit assessment about the drug (information for consent);
- furthermore, PL expected value – and the consequent information seeking behavior associated to it – can be examined in this framework as a function of its expected contribution to decision optimization.

## 2. Lay therapeutic decision

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<sup>544</sup> A decision under uncertainty differentiates from a decision under risk such as that of games of chance, where probabilities are objectively determined by the stochastic mechanisms underlying the game (1/6 probability for any die face in a throw, 1/52 of a Queen of hearts, etc.). However terminology slightly varies in the literature, especially objections are moved against the misleading use of the word “risk”: Gärdenfors, Sahlin, 1988: 5. Andersson and Littkens, 2002 use the term ‘conventional risk’ for uncertainty with known probabilities, in the sense that the individual is sufficiently confident to assign a specific probability measure to the events under consideration, and of ‘genuine uncertainty’ for a situation approaching ignorance, i.e. where the decision maker has a very vague or no idea about the probabilities which he should assign to the relevant events.

The application of Bayesian decision theory to therapeutic decisions has a long tradition in medical decision practice.<sup>545</sup>

Health economics has also soon recognized health decisions as a paradigmatic case of decisions under uncertainty and has modeled the demand for health and health information along the SEU principle.<sup>546</sup>

Indeed it seems that health choices approach the paradigm of decisions under ignorance: i.e. of decisions where the relevant states are assigned no specific probabilities: “The individual is likely to be highly uncertain if not completely ignorant about the probabilities involved. For example, he may be vaguely aware that there is a serious disease called leukaemia while having no idea of whether he is likely to get it and no idea about his possibilities to affect the likelihood of getting it”.<sup>547</sup> In order to account for the variance in the degree of epistemic ignorance, Andersson and Littkens (2002) have proposed a mixed model of health decisions composed of two components: a standard SEU function and a generalized expected utility function which represents the expected utility over the states to which the decision maker is not able to assign firm probabilities.

The first component is referred to as the function characterized by conventional risk, in the sense that each relevant state is assigned firm probabilities. The second component accounts for “genuine uncertainty”, in that it contains all states for which the subject has no precise idea as to their probability of occurrence.<sup>548</sup>

This is represented in the model through the weighting factor ( $0 \leq \gamma \leq 1$ ) which measures the degree of confidence in the accuracy of the probability function, and whose complementary ( $1 - \gamma$ ), corresponds to the weight given to the states to which the decision-maker cannot assign any probability measure:

$$U(a) = \gamma(a) \cdot \sum_s \pi_s(a) u(h^s, a) + (1 - \gamma(a)) \cdot u_0(a).^{549}$$

The formula models health decisions by representing the utility function as depending on the anticipated health status (h), where the health states are ranked according to the number of (quality adjusted) healthy days.

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<sup>545</sup> See for instance Green et al., 1998; Chapman, Sonnenberg, 2000. This tradition has a ‘prescriptive’ perspective: it aims at using Decision Analysis for making options as much explicit as possible in order to optimize medical resources and enable the practitioner to justify his choice on a rational basis (not ultimately as an argumentative point in case of litigation).

<sup>546</sup> The pioneering and influential article by Arrow (1963) has first emphasized the presence of uncertainty in choices related to health. Grossman (1972) has settled the principles for the tradition of studies on health demand. See for an introduction to the topic: Lindgren (2002) and Andersson and Littkens (2002) with related literature references.

<sup>547</sup> Andersson and Littkens (2002): 41.

<sup>548</sup> Andersson and Littkens (2002): 41.

<sup>549</sup> Andersson and Littkens (2002): 42; 45: “The interaction between risk and uncertainty aspects of the model seems to capture an important element in decisions about health related activities. Even when we are dealing with risk – so that an individual is implicitly thinking in terms of probability for, say, lung cancer – it seems reasonable to argue that he is often unsure about whether he has in fact the correct probability ( $\pi_s$ ) and about the effect of his actions on the probability of ill health ( $\partial\pi_s/\partial a$ ), e.g. the effect of smoking on the probability of lung cancer. The size of  $\gamma$  reflects the degree to which the individual is confident about  $\pi_s$  and  $\partial\pi_s/\partial a$  (though we cannot separate the two attitudes)”.

The first component is an ordinary expected utility function with a probability distribution over health states  $h_1$  through  $h_s$  (where  $h_n > h_{n+1}$ , i.e. preference decreases with cardinality). Both the utility and the probability function depend from the vector of activities (a):

- the probability function because of state-act dependency,
- the utility function because of the subjective cost associated to these activities.

The second component is a generalized expected utility. It refers to health states  $S + 1, \dots S + S'$ , for which the individual is not able to assign firm probabilities and  $u_0(a)$  is a reduced form of the expected utility over these states:<sup>550</sup>

$$u_0(a) = \tilde{E} \{u(h, a) \mid S + 1, \dots S + S'\}.$$

The weighting factor  $\gamma$  allows accounting for the effect of risk information which can simultaneously make people more genuinely uncertain (decrease of  $\gamma$ ) and more pessimistic regarding the probability of a specific disease (higher probabilities are associated to less preferred states in  $\pi_1(a), \dots \pi_s(a)$ ).<sup>551</sup> In general it serves to measure the degree of confidence in the probability distribution of firm states ( $h_1$  through  $h_s$ ).

An activity (a) makes the distribution more favorable if it induces a shift in the distribution in the direction of stochastic dominance.<sup>552</sup> Consequently the comparative utility of two health promoting (or risk preventing) activities should be assessed on the benchmark of their impact on the distribution in terms of stochastic dominance.

This model is based on the assumption of *uncertainty pessimism*: the states surrounded by genuine uncertainty (no probability attached) are also the worst in the ranking:  $h_{s+s'} < \dots < h_{s+2} < h_{s+1} < h_s$ . This assumption is realistic for modeling health demand in healthy individual (who might indeed be totally ignorant about the likelihood of being affected by a severe illness in the future). However, the therapeutic decision of a diseased patient might require further specifications. For the present purpose I will retain this assumption on the grounds that:

1. the first component of the utility function can be considered to reflect the information provided by the doctor (tailored benefit-risk magnitude and

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<sup>550</sup> Andersson and Littkens (2002): 43 and related footnote 5. These states are such that the agent does not have the roughest idea whether any preventive activity would influence their probability of occurrence: “As soon as the individual believes that it is possible to influence the probability of health outcomes – even if it is a very vague belief or hope – the probabilistic part of the function is involved”. Andersson and Littkens (2002): 46. *Uncertainty aversion* (ignorance denial) is captured by the assumption that states  $S + 1, \dots S + S'$  are assigned probabilities that need not sum to 1. When the estimation is computed however these are “normalized” and transformed into weights summing to 1:  $u_0(a) = \sum v_s u(h^s, a)$ .

<sup>551</sup> “If for example an exogenous event – like the alarm about the mad cow disease in Britain in 1996 – simultaneously makes people more genuinely uncertain and more dismal regarding the probability of brain disease, this is captured perfectly well by a simultaneous shift in the degree of uncertainty ( $\gamma$ ) and in the probabilities ( $\pi$ )”. Andersson and Littkens (2002): 43.

<sup>552</sup> i.e. if the cumulative distribution dependent on the activity  $a_i$  is such that:

$$F_{ai}(h; a) = \frac{\partial F(h; a)}{\partial a_i} \leq 0.$$

One distribution stochastically dominates another if for each outcome,  $h$ , something less preferred is less probable. The corresponding cumulative distribution functions for each should be such that for each  $h$ ,  $G(h) \leq F(h)$ . Andersson and Littkens, 2002: 45.

- probability data), while the second can reflect residual doubts generated by the doctor's or other information sources, for instance the PL;
2. whenever the PL informs the consumer of risks not previously addressed by the doctor, this information should be taken into account according to informed consent regulation (relevance assumption), but, given that it is not tailored to the individual it is doubtful whether it can be assigned accurate probabilities.<sup>553</sup> The more data about risks learned and surrounded by prognostic uncertainty, the more weight the second component of the utility function will have.

Although Andersson and Lyttkens' model has descriptive purposes, it can be also used as a benchmark for assessing the level of information accuracy at the basis of a decision, and eventually serve as a normative model for determining the extent to which the consent based on PL information can be considered informed.

In fact the legislator implies that the decision-maker should be aware of benefits, risks and probability thereof. Consequently the "genuine uncertainty" component should equal 0 for consent to be informed, or at least approach it.

*Following Andersson and Lyttkens' model, consent could be defined as informed to the extent that the decision maker can assign a probability measure to each health status ( $\gamma \rightarrow 1$ ) and can gauge whether the impact of the act  $a_i$  (undertake the therapy) makes the distribution more favorable with respect to  $a_j$  (do not undertake the therapy).*

As for the contribution of PL information in this respect, even if it is not supposed to give all details of the consequences of not taking the drug for the single individual (this information should indeed be provided by the doctor), still it is supposed to give essential data about  $a_i$ : take the drug.

Consequently PL information could be considered adequate for consent to the extent that  $\gamma$  for  $a_2$  approaches to 1, i.e. to the extent that all relevant health states are assigned a probability measure conditioned on the act of taking the drug. Provided the principle of proportionality for risk disclosure, the amount of  $\gamma$  should be greater,

1. the greater the therapy risk is;
2. the less severe the illness is;
3. the less probable the benefit is.

Moreover, consent will be considered informed in the measure that the probability distribution  $\pi_1(a), \dots, \pi_s(a)$  in relation to the anticipated health states approaches truth.

Furthermore, because the choice also depends on the expected utility associated with the act of taking the drug or not, the contribution of PL information should be measured also on the basis of its part in giving relevant information for the utility function  $u(h^s, a)$ , i.e. information about the magnitude of the drug benefit and of its potential damage.

## **2.1 PL information within the therapeutic decision**

The legislator implies that the decision to take a drug depends from the prognostic assessment of health benefit and risk. In accordance with the SEU model, the drug purchaser should evaluate the act of taking the drug vs. not taking it on the basis of

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<sup>553</sup> This point will be discussed further below.

the risk and benefit information provided in the PL. Following the model presented above, PL information should concern  $a_i$  (the act of taking the drug) and provide essential information both as to the utility and the probability attached to each possible outcome ( $h_{1-s}$ ).

PL benefit and risk data should allow the decision maker assign any possible health state a probability ( $\pi$ ) which depends on the act itself of taking the drug. The greater the confidence factor  $\gamma(a_i)$ , the more accurate is judged the probability distribution and the less relevant are health states surrounded by uncertainty.

The analysis of PL information will therefore focus on both benefit and risk information (with a special attention to risk information, which is preponderant in package leaflets) with respect to magnitude and probability.

The perspective of this investigation is not descriptive (modeling health information demand and effect in relation to package leaflets) but normative,<sup>554</sup> i.e. focused on the question whether this information is intrinsically capable of bringing its specific contribution to informed consent. A descriptive analysis of the effect of PL information, and of its expected value will be undertaken in the next chapter and in the empirical part of this work. The table illustrates the distinction between a normative and a descriptive analysis of PL information:

			Normative Evaluation of PL information as a basis for informed consent.	Descriptive Description and eventual modeling of PL information effect on drug users (e.g. lack of therapy compliance).
magnitude	Benefit		PL <u>epistemic value</u> as to the assessment of benefit and risk magnitude and probability	PL <u>effect</u> on the estimation of benefit and risk magnitude and probability - mediated by its <u>expected value through information processing granularity</u> .
	Damage			
probability	Benefit			
	Damage (Risk)	prognosis		
		diagnosis		

The normative analysis takes into account that the main responsibility for therapeutic information falls on the doctor and that it is assumed that doctor's information should supersede PL information, anytime the two differ, in that it is tailored to the individual (medical errors in prescription or information disregarded).<sup>555</sup>

## 2.2 PL information contribution to the decision utility function

As illustrated in the preceding paragraphs, the utility functions of taking vs. not taking the drug depend on the anticipated health outcome. PL information may increase accuracy by providing relevant data as to the short-medium-long term health implications of taking the drug both in terms of welfare improvement, and of

<sup>554</sup> For a further distinction between the “normative” and “prescriptive” use of Bayesian theory see: Bell et al. (1988b)

<sup>555</sup> I will illustrate this claim especially with reference to the frequency data associated with side effects.

potential damage (anticipated health outcome). The relevant parameters, which PL information should sharpen, are the probability function over the health states,  $\pi_s(a)$  and the utility function,  $u(h^s, a)$ , through data about probability and magnitude of drug benefits and risks.

### **2.2.1 Drug benefit magnitude**

The drug consumer indirectly evaluates the drug benefit on the basis of the disutility brought to him by the illness. This is why the drug risk/benefit evaluation has often been referred to as a risk/risk assessment (illness vs. drug risk). However this is not an accurate description in that the illness symptoms are certain, i.e. they are not a risk but an ongoing damage.

An exception to this state of affairs is constituted by treatments concerning specific “risk factors” such as high blood pressure (which enhances for instance the risk of heart stroke). In these cases the evaluation related to the therapeutic choice is indeed a risk/risk assessment.

Within the therapeutic decision the benefit information is principally provided by the doctor during prescription as the main rationale for consent giving. It is indeed implicit in the consultation dynamic that the drug prescribed at the end of the visit should alleviate or cure the condition which induced the patient to see the doctor. PL information constitutes in this context confirmatory information which can contribute to the modification of the utility function insofar as the drug information also includes the type of pharmaceutical effect (symptomatic vs. therapeutic) whenever this information has not been previously (and negligently) delivered by the doctor. Also information about eventual addiction effects or indication for other conditions in addition to one’s own disease can constitute valuable information whenever not already learned from the doctor. However, lack of benefit information from the doctor generally invalidates consent, and consequently the question of the role of PL information in this respect does not come into consideration.

### **2.2.2 Drug damage magnitude**

The assessment of risk magnitude is a function of the number and severity of side effects included in the PL. Magnitude assessment can be hindered by a series of factors which singularly and jointly constitute a barrier towards the understanding of the health implications related to the symptoms and effects mentioned in the warning list.

The following points display some of the difficulties which the reader might face in assessing the risk magnitude, when reading a specific side-effect in the warning list:

- a) uncertain implications of the symptoms (clinical-laboratory tests and blood serum modifications included);
- b) medical jargon;

c) pragmatic aspects of communication (invited inferences).<sup>556</sup>

a) The greatest uncertainty source is represented by the description of symptoms whose (eventual long-term) implications might not be clear for the reader. This leads to misunderstandings in both directions: light side-effects might unduly alarm the reader, because he draws false conclusions from their description, or vice versa, he might erroneously neglect severe side-effects and consider them as negligible (eventually failing to take adequate measures timely).

Example:

“Erkrankung der Nerven (Periphere Neuropathie)”.

“Nerves disease (peripheral Neuropathy)”.

What are the health implications of this side-effect? Is it a transitory disturbance or a permanent disease? What does it consist of?

Also difficult to gauge for a lay reader is the meaning of a laboratory test result concerning blood values (blood particles, sugar level, and liver values) or clinical kidney tests. The medical implications of such data are not part of his competence and therefore uncertainty might arise as to their interpretation. The same holds for information concerning changes in the cardio-circular system.<sup>557</sup>

b) A second source of uncertainty is medical jargon: terms like “lupus erythematosus” might not be associated to any adequate illness concept and so get simply not neatly categorized as either severe or light side effect. Although in this case we are speaking of a very severe side-effect, not many lay readers might get the message in its consequences.

c) Another source of uncertainty lies on a higher order level of text comprehension, the pragmatic conversation maxims. The maxim of order, which entails the reader interpreting a list of items as displaying a ranking among them (of increasing or decreasing importance for instance) is often violated by presenting the side effects list in an order that mismatches their ranking as to the degree of severity:

“Gelegentlich (0,1 – 1%): Lungenembolie, Atemnot (Dyspnoe), Wasseransammlung in der Lunge (Lungenödem), Nasenbluten (Epistaxis), Blutspucken (Hämoptysis) und Schluckauf”.

“Occasionally (0,1 – 1%): lung emboli, difficulty in breathing, water retention in the lungs (lung edema), nosebleed, blood spittle and hiccup”.

From the point of view of illocutionary commitment, there are several cases of “attenuated” warnings: Text passages, in which the PL formulae provide a piece of risk information with no clear illocutionary meaning. Here are some examples:

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<sup>556</sup> Linguistic analyses of package leaflet are presented in chapter 5. Here a brief list of main sources of uncertainty is presented in order to gauge the contribution of PL information with respect to the utility assessment of taking the drug vs. not taking it.

<sup>557</sup> In fact in some texts these side-effects are explicitly presented as concerning the physician’s diagnostics: “Darüber hinaus kann ihr Arzt EKG-Veränderungen sowie Herzrhythmusstörungen feststellen” (“Moreover, your physician can diagnose ECG-modifications and heart rhythmus disturbs”); “Ihr Arzt kann eine abnormal Anhäufung von Stoffen im Lungengewebe (pulmonale Infiltrate) feststellen” (“Your physician can diagnose an abnormal accumulation of material in the lung tissues [lung infiltrates]”).

- Sometimes the warning seems just scientific information for the purpose of knowledge sharing:

„Geringfügige Veränderungen des Blutzuckerspiegels und der Elektrolytwerte wurden selten beobachtet. Die klinische Bedeutung dieser Veränderungen bei sonst gesunden Patienten ist unklar“.

“Slight modifications of the level of blood sugar and electrolyte values have been seldom observed. The clinical meaning of these modifications is by otherwise healthy patients unclear”.

- In other cases a warning is at the same time communicated and neutralized:

„Häufig tritt eine Verminderung einer bestimmten Untergruppe der weißen Blutkörperchen (Neutropenie) auf, ohne dass sonstige Krankheitszeichen zu beobachten sind“ (Propycil 50 – Admeda).

“It occurs often a decrease of a specific subgroup (neutropenia), with no other observable signs of illness”

„Gelegentliche ... Gelenkschmerzen ohne erkennbare Gelenk-Entzündungszeichen“ (Propycil 50 – Admeda).

“Occasional articular pain without recognizable signs of articular inflammation”.

The assessment of potential damage is highly prejudiced by the lack of adequate indexing of damage magnitude, especially as far as medium to long term consequences on the organ system are concerned.<sup>558</sup>

In general improved communication, reader-friendliness and health literacy have a fundamental role in enabling the patient’s capacity to assess the therapy’s benefit and risk magnitude.

Increased health literacy – as partly promoted by the doctor during consultation – might moderately contribute to a personal appraisal of the drug risk potential in a specific situation. However it cannot absolutely cover all possible items of information contained in the PL. For these, the reader will be unable to assign any personal disutility measure as an appraisal of their significance.

## **2.3 PL information contribution to the probability distribution**

The therapeutic decision is considered informed to the extent that the patient can assign a probability function to the anticipated health status, and no health states are surrounded by uncertainty ( $\gamma \rightarrow 1$ ).

Moreover, this probability distribution should mirror as close as possible the real risk and benefit to which the patient is exposed to.

However, PL frequency information lacks of specificity with regard to the individual user and therefore does not enhance accuracy to the doctor’s risk-benefit assessment.

The contribution of frequency data in connection to those side-effects which have not been addressed by the doctor is positive but very low in terms of probabilistic accuracy.

### **2.3.1 Benefit probability**

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<sup>558</sup> See suggestions for improvement in Waller, Evans, 2003: 22.

Information about the drug benefit is generally given in the PL in assertive form, and therefore implicitly presented as certain. This can be in contrast to the trial and error attitude which guides many therapeutic decisions, where the doctor prescribes a treatment without being certain of the healing effects. Sometimes treatments are prescribed also with diagnostic purposes: if the patient reacts to the treatment, this can constitute favorable evidence that he is indeed affected by the illness which the drug is supposed to cure. In this sense, benefit information given as certain can induce false beliefs in the reader.

Anyway, efficacy data (the probability of healing effects) is also considered to be part of the doctor's information duty, and therefore PL information is not supposed to give any specific contribution to informed consent in this respect.

### 2.3.2 Damage probability: risk

Information about side effects frequency is derived from laboratory experiments, clinical studies and relevant literature on the topic. This information should represent the strength of association between a specific side effect and drug use.

Data about adverse drug reactions are derived from several statistical sources, whose degree of predictive value differ considerably: randomized control trials (RCT), observational studies, and pharmacosurveillance spontaneous reporting of adverse drug reactions. The evidence value of these types of studies depends on the experiment design, on the sample size, and on the type of side effect considered.

The experiment design should guarantee that the effect observed can be really ascribed to the parameter investigated and that possible confounders are neutralized through randomization or controlled through adjustment. Sample size warrants for representativeness of data with respect to the population of interest. Finally, different types of side effect (rare vs. frequent, short-term vs. long-term) require different types of experiment design in order to be detected and quantified.<sup>559</sup>

The strength of association between a cause and an effect is computed out of data about their joint occurrence, joint absence, and joint occurrence of one in the absence of the other:

	C	-C	
E	a	b	a+b
-E	c	d	c+d
	a+c	b+d	

The strength of association is directly proportional to cell a and d, and inversely proportional to cell b and c. It can be assessed through different measures (for instance by computing the odds:  $ad/bc$ ).

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<sup>559</sup> For an epistemological discussion on the evidence value of RCTs with respect to other methodological approaches in the natural and social sciences see: Cartwright, 2007.

In clinical trials  $a/a+c$  is compared to the control datum  $b/b+d$  relative to the effect observed in absence of drug use (generally a placebo), in order to assess the treatment efficacy with respect to the control.<sup>560</sup>

In the case of side effects the strength of association between a certain side effect and a specific drug is generally represented by the difference of side effect incidence in the users group with respect to non-users:

The following contingency table presents a hypothetical example:<sup>561</sup>

	Drug	¬Drug	
Side effect	.01	.03	.04
¬Side effect	.02	.94	.96
	.03	.97	

$$\text{Strength of association between drug and side effect} = P(S/D) - P(S/\neg D) = \frac{P(S\&D)}{P(D)} - \frac{P(S/\neg D)}{P(\neg D)} = \frac{.01}{.03} - \frac{.03}{.97} = .33 - .0303 = .327$$

In order to dispose of all the cell data, information about the proportion of sample population exposed to the drug with respect to population is necessary. This information is available in clinical trials and observational studies with a control group, but not in pharmacosurveillance data. However each type of study has advantages and shortcomings with respect to the others:

I. Clinical trials provide a good control of confounders through randomization,<sup>562</sup> however their results should be evaluated in consideration of three fundamental aspects:

1. They are not representative of the user's population because the recruitment cannot account for multimorbidity cases, elderly subjects and in general the combination of factors present in clinical setting. Therefore the generalizability of these findings to ordinary practice is not guaranteed by the study.<sup>563</sup>
2. They are based on relatively little samples. This heightens the probability of excluding persons of higher susceptibility than average and results in the failure to detect rare, particularly type B (non-pharmacologically mediated) adverse drug reactions.<sup>564</sup>
3. Clinical trials cannot detect long-term side effects due to prolonged drug use.

II. Observational studies, especially cohort studies, range over a longer period and/or are based on a large population but are compromised by lack of randomization, and therefore cannot completely control for confounders.<sup>565</sup> This means that the proportions in the cells could reflect the hidden effect of some confounding factor rather than the effect of the treatment itself.

<sup>560</sup> The traditional asymmetry in efficacy vs. risk research is especially reflected in the insufficient investigation of side effects in randomized control trials. See Steckelberg, 2005: 345; Waller, Ebans, 2003: 20; Wilcken, 2007: 370.

<sup>561</sup> For an introduction to the interpretation of contingency tables within the framework of pharmacoepidemiology see Bender, 2001.

<sup>562</sup> Bartons, 2000: 256.

<sup>563</sup> Waller, Evans, 2003: 20; Wilcken et al., 2007: 368.

<sup>564</sup> Waller, Evans, 2003: 20.

<sup>565</sup> Barton, 2000: 255.

III. Postmarketing surveillance data lacks both randomization and control. Confounders are only partly controlled through a selection of ADR reports on the basis of a causal assessment,<sup>566</sup> and there are seldom epidemiological data about drug exposure which provide the basis for incidence assessment.<sup>567</sup>

Furthermore, pharmacosurveillance data are statistically flawed because of practical reasons. Post-marketing surveillance is blamed to be affected by underreporting and lack of standardization in symptoms description and causal assessment. From the point of view of evidence based medicine criteria, pharmacosurveillance tends to rely considerably on low quality evidence with respect to hierarchies.<sup>568</sup>

The observed variance in the prescription materials (SPC, PL, data sheets) available for the same drug in different countries – and within the same country among different brands of the same drug –<sup>569</sup> constitute an indirect proof that evidence for each single drug happens to be collected, assessed and evaluated differently in different environments.

The epistemic value of side effects probabilistic information is therefore very limited as to its *accuracy* – because data coming from pharmacosurveillance are not supported by epidemiological data about drug exposure and relevant alternative risk factors, and observational study cannot completely control confounding – and *exhaustiveness* – because clinical trials cannot detect rare and long term side effects. A shortcut to the lack of adequate data for a precise estimation of side effect occurrence is the broad categorization into which frequency estimates – as proposed by the legislator – are slotted in:

- > 10%
- 1 – 10%
- .1 – 1%
- .01 - .1%
- < .001%

The probability interval of any side effect in each of the five levels falls in a considerably large range. As a consequence, PL information about side effect frequency is also *vague*.

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<sup>566</sup> See chapter 1. § 4.2. Pharmacosurveillance retains however an indispensable value as a detection system. Waller, Evans, 2003: 20.

<sup>567</sup> Talbot, Nilsson, 1998: 429.

<sup>568</sup> Waller and Evans, 2003: 19. A paradigmatic case can illustrate this claim vividly. In the 1930s, soon after amidopyrine was identified as a cause of agranulocytosis, also dipyrone was, and cross-sensitivity between the two components was demonstrated: *the incidence of agranulocytosis was assumed for both substances to reach a proportion of 1 out of 120 treated patients*. Given this association the drug was banned in most industrialized countries (but it is still available in Germany, France and Spain). This assessment was questioned and reduced as low as *1.1 case per million* users along the results of an international case-control study (International Agranulocytosis and Aplastic Anaemia IAAA). In Sweden the drug had been withdrawn from the market on March 1974 due to an estimated incidence of *1 case in 3000 patients* and commercialized again from 1995 onwards because of the low incidence found in the IAAA research. In 1999 it was again suspended thanks to a study conducted on the basis of all ADRs reports to the Swedish Adverse Drug Reactions Advisory Committee in the period 1966-1999, which assessed the risk at *1 out of 1:1439* (C.I. 95%: 1:850 to 1:4684). Along its commercial history, dipyrone has been associated with a largely variable range of frequency estimations with respect to its association with agranulocytosis: this variance illustrates the problems inherent with the assessment of drug risk probability. Hedenmalm, Spigset, 2002.

<sup>569</sup> Reggi et al., 2003.

Low accuracy, non exhaustiveness and vagueness are amplified when it comes to the individual risk prognosis for the single drug consumer.

### 2.3.2.1 PL information and individual risk

It is acknowledged in pharmacological literature that both drug efficacy<sup>570</sup> and risk is strongly dependent on the individual susceptibility to the drug (given dosage and therapy duration): “risk is not evenly distributed ... Some patients are at very high risk and others at essentially zero risk, the challenge is to define that individual risk”<sup>571</sup>.

Age<sup>572</sup>, sex, genetic make up, physiological changes, exogenous factors (drug-drug or food-drug interference) and disease-drug interaction influence the patient’s susceptibility to adverse drug reactions. Also ethnicity seems to be a carrier of factors (environment, genetics, lifestyle) determining higher or lower susceptibility to drug efficacy<sup>573</sup> and side effects as well.<sup>574</sup>

The table below presents paradigmatic cases of altered susceptibility to adverse drug reactions:

Sources of susceptibility	Examples	Related literature
Genetic	Porphyria	
	Succinylcholine sensitivity	
	Malignant hyperthermia	
	CYP isozyme polymorphisms	
Age	Neonates (chloramphenicol)	Mulhall A., de Louvois J., Hurley R. Chloramphenicol toxicity in neonates: its incidence and prevention. <i>BMJ</i> , 1983; 287: 1424-7.
	Elderly people (hypnotics)	Greenblatt D.J., Divoll M., Harmatz J.S., MacLaughlin D.S., Shader R.I. Kinetics and clinical effects of flurazepam in young and elderly noninsomniacs. <i>Clin Pharmacol Ther</i> , 1981; 30: 475-86.
Sex	Alcohol intoxication	
	Mefloquine,	Schwartz E., Potasman I., Rotenberg M., Almong S., Sadetzki

<sup>570</sup> Goldstein et al. 2007.

<sup>571</sup> Spielberg, 1993: 31, 32. See also Waller, Evans, 2003:22. For the implications related to the communication of risk probability in these settings see Calman, 1996.

<sup>572</sup> The risk of contact allergy to neomycin sulfate seems for instance to vary with age and increase with the number of additional positive reactions to other standard series allergens. Menezes de Pádua et al. (2005).

<sup>573</sup> “Ethnic group may act as a marker for underlying genetic or environmental differences in this susceptibility” McDowell et al. (2006): 4. McDowell et al. (2006): 1. Relevant cases with regard to this point are the recent approval of isosorbide dinitrate plus hydralazine (BiDil) specifically for use in black patients: McDowell et al. (2006): 1.

<sup>574</sup> A meta-analysis on the literature devoted to the investigation of the relationship between ethnicity and ADRs to cardiovascular drugs has for instance delivered the result that the relative risk of angio-oedema from ACE (angiotensin converting enzyme) inhibitors in black patients is 3.0 compared to non-black patients(C.I. 95%: 2.5 to 3.7); the relative risk of cough in concomitance with ACE inhibitors is 2.7 when compared between East-Asians and white patients(C.I. 95%: 1.6 to 4.5); and the relative risk of intracranial haemorrhage with thrombolytic therapy is 1.5 (C.I. 95%: 1.2 to 1.9). McDowell et al. (2006): 2-3. See also Henry et al., 1996 for gastrointestinal reactions to NSADs. The cited literature intends by no way to exhaust the literature on drug susceptibility variance, which is lately continuously gaining importance also as a consequence of the contributions coming from pharmacogenomics.

	neuropsychiatric effects	S. Serious adverse events of mefloquine in relation to blood level and gender. Am J trop Med Hyg 2001; 65: 189-92.
	Angiotensin converting enzyme inhibitors, cough	
	Lupus-like syndrome	Batchelor J.R., Welsh K.I., Tino R.M., Dollery C.T., Hughes G.R., Bernstein R. et al. Hydralazine-induced systemic lupus erythematosus: influence of HLA-DR and sex on susceptibility. Lancet, 1980; i: 1107-9.
Physiology altered	Phenytoin in pregnancy	Dickinson R.G., Hooper W.D., Wood B., Lander C.M., Eadie M.J. The effect of pregnancy in humans on the pharmacokinetics of stable isotope labeled phenytoin. Br J Clin Pharmacol, 1989; 28: 17-27.
Exogenous factors	Drug interactions	
	Interactions with food (e.g. grapefruit juice with drugs cleared by CYP3A4)	Aronson J.K., Forbidden fruit. Nature Med, 2001; 7: 7-8.
Disease	Renal insufficiency (e.g. lithium)	Clericetti, N., Beretta-Piccoli C., Lithium clearance in patients with chronic renal diseases. Clin Nephrol 1991;36: 281-9.
	Hepatic cirrhosis (e.g. morphine)	Hasselstrom J., Eriksson S., Persson, A., Rane A., Svensson J.O., Sawe J. The metabolism and bioavailability of morphine in patients with severe liver cirrhosis. Br j Clin Pharmacol 1990; 29: 289-97.

**Table 5: Examples of drug risk variability determinants (Source: Aronson, Ferner, 2003: 1223).**

The individual degree of susceptibility to a specific drug depends on the combination of the diverse parameters: conditional on their personal health profile, two individuals can show dramatic different reactions to the same molecular entity.

The level of personal susceptibility cannot be obviously taken into account in product information. As a consequence, PL frequency data might be not very informative for the individual facing a therapeutic decision.

The combination of the parameters determining the individual level of susceptibility is potentially infinite and therefore its effect in terms of individual susceptibility to a specific product cannot feasibly be anticipated in product information, but can at most be assessed by the health professional in possession of all relevant data both about the drug and the individual at stake (age, sex, genetic predispositions, health history, standard of living).

In a formula, the probability of side effect occurrence should be computed out of drug toxicity information (SPC and PL among other sources), quantity (dosage and duration) and personal susceptibility:

$$P(SE) = P(DT = i, Q = l, PS = h),^{575}$$

<sup>575</sup> Because drug toxicity and personal sensitivity are given, while dosage (Q) can be calibrated at will, the probabilistic formula for assessing the personal probability of a side effect, could be also reformulated in counterfactual language:  $P(SE_x/\text{take drug } y) = P(Q_i \square \rightarrow SE_x/(DT = I; PS = h))$ .

A counterfactual is a belief entertained by an agent about the causal relation between an act  $a_i$  and its capacity to bring about state  $S_i$ . The symbol used for the counterfactual relation is:  $\square \rightarrow$ . "I do a  $\square \rightarrow S$ " should be read: "If I were to do a, then S would hold". Let a world  $W_a$  be the most close to the actual world at time t, if  $W_a$  is the world which unfolds after time t in such a way that if "I do a" is true in  $W_a$ , then "I do a  $\square \rightarrow S$ " is true iff S is true in  $W_a$ . Causal decision theory has emerged in order to account for the so called Newcomb paradox by distinguishing between evidentiary value of an act as a symptom that some state will obtain and its genuine contribution to the state occurrence. Gibbard, Harper, 1988 (1978): 342. Lewis has underlined that indeed *even when independency between acts and states can be assumed, precisely because of this assumption "the full story" is causal* (Lewis, 1988: 377). However, even if the distinction between causal and symptomatic state-act dependency has fundamental implications for the

Where the level of drug toxicity (DT = i) also depends on dosage and duration (Quantity Q = l) and the level of personal susceptibility to the drug components (PS = h) depends from both drug toxicity and quantity:

$$= P(DT = i/Q = l) \times P(PS = h/DT = i; Q = l).$$

The integration of PL data with relevant parameters is however out of the lay reader's competence (and indeed very challenging for the health professional too). The legislator implicitly recognizes this state of affair by invoking the doctor's responsibility in assessing the *personal risk/benefit assessment specific to the individual patient*.<sup>576</sup>

The doctor is deemed responsible for checking the patient's personal susceptibility on the basis of his genetic parameters, his health history, clinical profile, lifestyle and actual health conditions. He is responsible for prescribing him a therapy with an *individually favorable* risk/benefit assessment and for communicating him both risks and benefits associated with the therapy.<sup>577</sup>

It is therefore his task to evaluate the individual risk and positive response to the drug, so as to make a rational choice.

The doctor's information cannot cover all items contained in the PL though. Indeed, the majority of the side effects listed in the PL are not generally addressed by the doctor – in consideration of their negligibility in relation to the patient at hand.

However, even if the eventuality of these side effects is not explicitly considered by the doctor, still the patient must take them into account in his choice, because however negligible, their occurrence cannot be excluded with absolute safety.

But, as the above considerations show, PL frequency data are not informative as to the actual risk to which the individual is exposed and the patient is not in the position to tailor PL information to his risk profile. Thus, their contribution to risk assessment is questionable. The probability assignment  $\pi_s(a)$  would not get closer to truth by taking PL frequency information as a best estimate of one's own risk exposure. Eventually, the awareness of this fact would also impact the degree of uncertainty ( $\gamma$ ). Indeed *each side effect mentioned in the list raises the question as to its possible occurrence, a question which the probabilistic data associated to it only marginally help answer*. Given that the patient is hardly able to select which side effects are going to affect him, this information is bound to enter in the second component of the utility function and increase genuine uncertainty (thereby decreasing  $\gamma$ ).

### 3. PL information as an alerting device

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mathematical model proposed by Savage, it has no repercussion at the level of probability computation, and therefore can be left apart in this context.

<sup>576</sup> In the U.S. the theory of the learned intermediary relates precisely to the inadequacy of product information as a basis for individual prognosis: the doctor intermediates between the pharmaceutical firm and the drug consumer by selecting the appropriate product on the basis of an individual risk/benefit assessment and is also supposed to be in the best position for informing the consumer about his personal risk/benefit prognosis. See Ferguson, 1992, for discussion.

<sup>577</sup> See chapter 4 § 2.

The analysis of PL information with respect to its potential contribution to the decision parameters (degree of accuracy  $\gamma$ , probability distribution  $\pi_s(a)$ , utility function  $u(h^s, a)$ ) has delivered following results:

1. Most information is surrounded by uncertainty in terms of magnitude (health implications in the medium to long term effects).  
Because utility is defined in terms of quality adjusted health states, lack of clarity about the health implications related to drug intake constitutes an insurmountable obstacle to the integration of PL data in the decision maker's utility function  $u(h^s, a)$ . Therefore these data will either fail to be taken into account or contribute to increase the weight of the second component of the utility function, thereby increasing genuine uncertainty (therefore decreasing  $\gamma$ );
2. Also probabilistic information does not help the reader increase his accuracy in terms of personal risk exposure: the frequency data resulting from clinical trials, observational studies and pharmacosurveillance reports have a low predictive value in relation to the single user. For this reason all side effects not previously addressed by the doctor cannot be assigned an accurate probability ( $\pi_s$ ). These should therefore contribute to increase the weight of the second component of the utility function, correspondingly decreasing  $\gamma$ .
3. As for benefit probability data, they are generally given as certain thereby misrepresenting the fact that not only side effects, but also efficacy is dependent on the user's susceptibility. This leads to the construction of a probability distribution which fails to take into account benefit uncertainty (fallacious  $\pi_s$ ).

Along these observations it is hard to define the therapeutic choice made on the basis of PL information as "informed".

Indeed the epistemic status of PL information can be rather compared to that of an alerting device: risk data contained in the PL and previously not contemplated in the therapeutic decision made with the doctor cannot be assigned an accurate probability measure and therefore decrease  $\gamma$ . Furthermore, given the high preponderance of risk over benefit information, they are able to shift the median of the probability distribution towards the worst health states.

This double effect is at the origin of much research on the psychological effects of health risk information and will be treated in the last chapter.

#### **4. PL information and therapeutic safety**

The value of PL information as a risk prevention/minimization tool should not be hidden away by the above exposed considerations about the role of PL information for informed consent.

In fact, as an expert of his own health history the patient should be considered responsible for checking all information regarding adequate precautionary behavior (precautions, and eventually also contraindications) and notify the doctor about related facts who he might not know of. Avoidable risk *totally* depends on the user's (and the doctor's) behavior per definition.

Also information about side effects, which is to be considered information for consent in that it discloses residual (unavoidable) risk, can be contextually considered as safety information. The side effect list might help the reader identify an unexpected symptom eventually occurring during the therapy as drug conditioned rather than caused by the illness. This awareness might than help him take adequate countermeasures and call for the doctor up to eventually stop the cure.

In this sense, PL information can be considered as a support to diagnosis:<sup>578</sup> when the consumer is already taking the drug, the list of side-effects with associated frequencies might help the consumer consider the possibility that the origin of the unexpected occurring symptom is (more probably) associated to the drug than to the illness itself or to other factors, and act consequently.

Finally, PL information contributes to drug safety also indirectly by recommending the user to notify to his doctor or pharmacist any adverse reaction which is not written in the leaflet.<sup>579</sup>

In this second sense the drug consumer functions, as it were, as a terminal for the pharmaco-surveillance detection system,<sup>580</sup> and the PL message raises the awareness that the side effect list is not exhaustive.

## **5. Consequences for the legislator**

The distinct contribution brought about by PL information as a basis for prognosis (and therefore therapy consent) vs. its role in risk minimization/prevention (safety function) should be acknowledged by the legislator through adequate articulation of the liability distribution.

In particular, the patient's responsibility of taking notice of risk information should be emphasized as far as its preventing function is concerned. In this sense, also the list of side-effects can be considered safety information when consulted as a reference for identifying the origin of an unexpected symptom.

Whenever damage occurs which could have been prevented or minimized if the patient would have taken notice of precautions and warnings written in the PL, then he should be deemed responsible for (contributory) negligence.

This is also the case of unavoidable risk (side-effects) when recognized in time to hinder severe damage. In this respect information about side-effects accomplishes a safety function with respect to which the patient should be considered partly responsible.

Instead, failing to take notice of residual risk information as a basis for therapeutic choice cannot be equated to an information waiver as proposed by some legal theorists in analogy to doctor's liability.<sup>581</sup>

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<sup>578</sup> See also Amery, 1999: 125.

<sup>579</sup> As prescribed both by the European – Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use Art. 59 (e): OJ L 311, 28.11.2001: 86 – and by the German legislator (§ 11 I 5 AMG).

<sup>580</sup> Indeed, the introduction of a molecular entity into the market has been compared to a “population experiment”: Berger, Mühlhauser, 2000:155; Stricker, Psaty: 2004: 44). Some treatments are retired from the market even decennials after their approval: in a recent French study on product withdrawal, market life has been estimated on average 25.2 years for drugs with type-B ADRs, and 38.9 years for drugs with type-A ADRs (Olivier, Montastruc, 2006: 809).

<sup>581</sup> Koyuncu 2006 a. o.

In fact, PL information cannot be readily considered an adequate basis for an individual prognosis such as that provided by the doctor. Instead it only functions as an alerting device, which put the reader into notice about the risks observed to be associated with the drug in clinical trials, observational studies and pharmaco-surveillance. The frequency data emerging from these studies though are provisory and susceptible to continuous revision, because of the limitation inherent to their design: either they are non-representativeness because of limited sample size (RCTs) or they lack of control over confounders because of lack randomization and of control groups (observational studies, pharmaco-surveillance reports). More importantly the accuracy of these frequency data as predictors of risk for the individual is very limited, given the significant differences in drug susceptibility across risk groups and from individual to individual.

However, consent is informed to the extent that the consent-giver is made aware not only of the potential damage and risk, but also of its probability of occurrence. Therefore the consumer should not be considered committable to residual risk on the basis of PL information.

## **6. Summary and conclusion**

This chapter has undertaken the task of answering the following questions:

3. What requirements the legislator establishes for consent to be qualified as informed;
4. Whether PL information fulfils these requirements.

As for the first point, the requirements are derived from the right which the institute of informed consent should honor, i.e. the right to self-determination: Information prior to consent should enable the patient to make an autonomous choice and therefore provide him with relevant data about the intervention/therapy and the risks and benefits involved. In order to allow a risk/benefit prognosis also probabilistic data about the therapeutic effect and potential damage should be given.

In order to analyze the role of PL information in this setting, it has been considered its role as a contributor to epistemic accuracy within the therapeutic choice. The introduction of a Bayesian model for health choices accounting for the presence of genuine uncertainty (Andersson and Littkens, 2002) has allowed us to identify and distinguish relevant parameters in relation to the role of information in health decisions. The model is constituted by a two-components function. The first component is a traditional expected utility function (where utilities are weighted by probability assignments); the second is a generalized expected utility where health statuses (utilities) are surrounded by “genuine uncertainty” (tending to ignorance) and cannot be assigned firm probabilities.

Along this model, consent has been defined to be informed to the extent that it approaches a decision under risk (known probabilities), i.e. to the extent that the decision maker can assign a probability measure to each relevant health state in a ranking from the most favorable to the worst – being health states nothing else then

quantities of quality adjusted healthy days – and that he knows whether the act of taking the drug (a) shifts the probabilistic distribution towards stochastic dominance with respect to the act of not taking the drug.

This means that the weight factor associated to the first component of the utility function (which assigns a probability measure to each health status) tends to 1 ( $\gamma \rightarrow 1$ ) in the case where the decision is “informed”.

Against the framework of this model, PL information seems to provide the drug consumer with data whose personal relevance, and therefore prognostic value for the individual, is difficult to assess.

There are in fact no legitimate epistemic grounds for directly assuming the statistical frequency associated with side effects in the PL as a prognostic judgment about the probability that a single user might be concerned by the side effect.

In order for it to ground the prognostic assessment, PL information should be integrated with other parameters such as personal susceptibility given dosage/duration. This is precisely the task accomplished by the doctor when he discloses the therapeutic residual risk. However, the doctor is not supposed to inform the patient about all possible side effects contained in the PL, but only about those that he considers concretely possible in the single case.

Given that all side effects must however be taken into account by the drug user in accordance to the responsibility shouldered within informed consent, these data are bound to contribute to the weight factor assigned to the uncertainty component of the utility function.

Furthermore the probabilistic assessment should be combined with the perceived importance of the eventual damage (subjective disutility), the evaluation of which is most of the times hindered by the lay incompetence to appraise the magnitude and health implications of the risks mentioned in the PL.

This means that consent on the basis of PL information rather approaches a decision under ignorance than one under risk: as a prognostic device, PL information fundamentally asks more questions than it answers.

Given that the legislator implies that consent is given with knowledge of the probabilities of risks and benefits, PL information cannot be considered adequate for consent.

As for the safety function which PL information should also accomplish, the contribution of PL information in this respect does meet the minimal legal requirements, in that the drug consumer can actually profit from it in order to use the product correctly and safely insofar as instructions comply with readability standards established by the law. In this respect, also information about residual risk (side effects) accomplishes a safety function in that it might help the consumer identify eventual unexpected symptoms as side effects, whenever they are already listed in the text.

The legislator should account for this asymmetry and regulate liability clauses consequently: the consumer should not be considered committable to residual risk on the basis of PL information, but instead it should be emphasized his contributory negligence whenever safety aspects of PL information are not sufficiently taken into account by him.

# **PART III**

## **Empirical Findings**



# 7 **PL information and therapeutic choice: An exploratory study**

## **1. Introduction**

The preceding chapter has been devoted to a normative analysis of PL information and to demonstrate its different contribution to risk prognosis and diagnosis respectively.

It results that from a mere epistemic perspective PL information cannot constitute a valid reference for the individual assessment of risk and benefit prognosis.

Instead, it can eventually bring a valid contribution to the causal assessment of unexpected symptoms occurring during the therapy (diagnostic value).

The conclusion is that PL information cannot be considered as a valid support for the consumer's autonomous decision, but that it can validly help the consumer diagnose unexpected symptoms and act consequently. In this respect, the side effect list accomplishes a safety function in that it allows the patient take adequate measures for minimizing adverse drug reactions.

As a consequence, we have proposed that, corresponding to the different purposes of PL information, i.e. risk prevention/minimization (safety aspect) and risk disclosure (self-determination aspect), liability regulation should be correspondingly articulated into two distinct sectors. Failure to comply with safety information should indeed be categorized as (contributory) negligence from the side of the drug consumer. Instead, the simple disclosure of side effects in the PL cannot be considered as an adequate basis for informed consent and therefore cannot completely offload the pharmaceutical firm from responsibility about health damage.

The common objection to the qualification of PL information as a valid source for an autonomous decision moved in the legal literature and jurisprudence does not touch its epistemic foundations though, but rather takes into account psychological

considerations related to the effective fruition of this sort of information by the lay user.<sup>582</sup>

This type of objection is echoed for instance in court decisions which consider invalid the consent obtained through standardized formularies and generally written pre-drafted communication.<sup>583</sup> In the specific case of PL information, this attitude is mirrored in the latest pronouncement of the BGH concerning health damage compensation on the basis of information insufficiency: the information contained in the PL is not considered information for self-determination, so that the doctor is cautioned that a simple reference to the PL does not absolve him from the duty to inform the patient personally, because he cannot take for granted that *the patient will read and follow the instructions contained in the PL*.<sup>584</sup>

On the other side, legal theorists and the health professional alike raise a somehow opposite objection to PL information: this regards the frightening potential of PL information and its detrimental effects on compliance and therapeutic safety. Patients are assumed to get anxious about the therapy *by reading the PL* and consequently suspend the therapy.

Indeed, as already emphasized by the analyses conducted by linguists, given the uncertainty sources identified by them at all discourse levels (lexical, semantic, and pragmatic)<sup>585</sup> an ideal reader, should at least loose part of his confidence in the therapy, when not straightforwardly refuse it.

Empirical data about drug waste could be an indirect evidence of this reaction: each year 100 tons of pharmaceuticals for a value of 500 Mio. Euros go into the garbage. It is estimated that 1/5 to 1/3 of the prescribed drugs are thrown away without even opening the blister.<sup>586</sup>

However, a variety of responses to PL information has been empirically observed. A recent study on PL information evaluation conducted by the Wissenschaftliches Institut der AOK (WidO) reported 29% of the participants being less confident (“verunsichert”) after reading the PL.<sup>587</sup> This is a considerable figure, but still does not provide evidence of a general decrease in therapeutic confidence.

This chapter presents a quantitative study (of limited sample size: n = 55)<sup>588</sup> with the aim to explore PL information as basis for the therapeutic decision. A sort of “paired comparisons test” has been devised. Questions related to the risk/benefit estimation and decision confidence were asked before and after reading the PL accompanying the drug.

Bayesian categories such as knowledge updating, expected net value of information and decision sensitivity to further information have been integrated with specific dimensions concerning the therapeutic decision: trust in the doctor, shared decision making, experience with treatments and side effects.

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<sup>582</sup> See also chapter 4 § 4.5

<sup>583</sup> BGH NJW 2000, 1784, 1787, f; BGH NJW 1985, 1399; BGH VersR 1973, 244 (246); VersR 1985, 361 (362).

<sup>584</sup> BGH 15. 3. 2005, NJW 2005, 1717

<sup>585</sup> See chapter 5.

<sup>586</sup> Bronder, Klimpel: 2001. See chapter 4 § 4.5.

<sup>587</sup> Nink, Schröder, 2006: 76.

<sup>588</sup> The original version of the questionnaire can be found in the appendix.

## 1.1 Method

Like most empirical surveys many efforts had to be devoted to sample recruiting. In this case the difficulties were also increased because of the restricted relevant population: people under treatment at the time of survey, but not hospitalized. This choice was determined by the investigation purpose. In fact only people really concerned by the drawbacks of the illness can make a risk/benefit assessment in relation to the drug.<sup>589</sup> On the other side, I wanted to check the use of PL information in out-patients because its importance is very reduced in hospitalized patients, who anyway are seldom given the package leaflet of the drugs they are taking.

The questionnaire was administered in the university campus of Bielefeld in the period April-June, 2005. Participants were asked whether they wanted to take part in a survey concerning package leaflets and drug information, with the condition that they were actually taking a treatment. Most of the people contacted were not under treatment, but among the ones who were (ca.10%) I had a considerable feedback (82%). People were contacted in the university campus among the personnel and among students. Students were contacted in the mensa, and personnel was contacted in their bureaus. Reliability (avoidance of selection bias) could be partly secured by the fact that most of them participated because of the circumstance that it was a study conducted by the university in which they studied/worked, rather than for personal reasons.

Among them also a series of structured interviews were made (15) for the qualitative part of the study.

## 1.2 Sample population

The sample population is composed of 55 participants under therapy at the time of the survey. The distribution of treatment types is rather heterogeneous, as the table can show, but two main groups are preponderantly represented: antibiotics and blood pressure drugs. Blood pressure medication is subdivided in three beta-blockers, two angiotensin antagonists, two vasodilators, one ACE inhibitor, one calcium canal blocker, one anti-cholesterol medicament and one other treatment for which only the indication but no name has been provided by the participant.

Drug Type	Frequency
blood pressure	11
antibiotics	10
thyroid	5
non-steroidal antiinflammatory drugs (NSAIDs)	5
antihistamines	3
cortisone	3

Drug Type	Frequency
Antidepressant	2
pill	2
antiestrogen	2
anticoagulant	2
osteoporosis	2
asthma	2
benzodiazepin	2
other	4
Total	55

<sup>589</sup> See also Schuldt, 1992: 120; Edwards et al., 2003: 702.

According to therapy duration, the cases were classified as chronic (n = 31, more than 6 months since therapy inception) or acute (n = 24, less than six months). The time scope among the chronic cases is very large ranging from the 1<sup>st</sup> January 1975 until 20<sup>th</sup> June 2005. Among the acute cases, the relative majority of them are distributed in the first week.

**Acute cases: therapy inception time**

Therapy inception time	Frequency
≤ 1 week	11
≤ 2 weeks	2
≤ 2 months	3
≤ 3 months	4
≤ 4 months	2
≤ 6 months	2
Total	24

As for demographic data, the majority of the sample population is composed of female subjects (n = 42 against 13 male subjects). This reflects the preponderance of medication in female population.<sup>590</sup> Age has a “bimodal” distribution along the entire adult life span.

**Age**

Age group	Frequency	Percent	Cumulative Percent
17 to 20	2	3,6	3,6
20 to 29	10	18,2	21,8
30 to 39	7	12,7	34,5
40 to 49	12	21,8	56,4
50 to 59	9	16,4	72,7
60 to 69	7	12,7	85,5
70 or more	8	14,5	100,0
Total	55	100,0	

The sample is mainly composed of medium-to-highly educated persons, which is also reflected in the profession variable.

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<sup>590</sup> In recent studies the difference in drug use according to sex lies between 36% and 50% more consumption for women (with a higher gap for psychotic drugs). Knopf, H; Melchert H.-U. (1999) Subjektive Angaben zur täglichen Anwendung ausgewählter Arzneimittelgruppen- Erste Ergebnisse des Bundes-Gesundheitssurveys 1998. In: Das Gesundheitswesen 61, Sonderheft, 2: 151; cited in Krudop-Scholz, 2005: 38.

Education	Freq.	Valid Percent
Hauptschulabschluss (primary school)	11	20,8
Realschulabschluss (secondary school)	11	20,8
Abitur (secondary school)	15	28,3
Universität (University degree)	11	20,8
Other	2	3,8
Medicine student	3	5,7
Total	53	100,0
Missing	2	
Total	55	

Profession	Freq.	Valid percent
blue collar	5	9,3
<b>white collar</b>	14	<b>25,9</b>
<b>executive officer</b>	4	7,4
free lance	1	1,9
housewife	4	7,4
<b>Student</b>	13	<b>24,1</b>
health professional	6	11,1
other	7	13,0
Total	54	100,0
Missing	1	
Total	55	

As far as the health condition is concerned, this parameter has been measured by two questions:

- number and severity of diseases affecting the participant apart from the one for which the subject was under treatment with the drug related to the questionnaire (Q. 72):

health condition: number of diseases					health condition: severity of diseases						
		Frequency	Percent	Valid Percent	Cumulative Percent			Frequency	Percent	Valid Percent	Cumulative Percent
Valid	one	32	58,2	65,3	65,3	Valid	light	16	29,1	32,7	32,7
	> 1	17	30,9	34,7	100,0		severe	6	10,9	12,2	44,9
	Total	49	89,1	100,0			chronic	27	49,1	55,1	100,0
Missing	System	6	10,9				Total	49	89,1	100,0	
Total		55	100,0			Missing	System	6	10,9		
						Total		55	100,0		

- the number of other drugs, apart from the one for which the subject was making the questionnaire (Q. 74):

other drugs: how many					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	,00	29	52,7	53,7	53,7
	1,00	8	14,5	14,8	68,5
	2,00	3	5,5	5,6	74,1
	3,00	5	9,1	9,3	83,3
	4,00	4	7,3	7,4	90,7
	6,00	2	3,6	3,7	94,4
	7,00	1	1,8	1,9	96,3
	8,00	2	3,6	3,7	100,0
	Total	54	98,2	100,0	
Missing	System	1	1,8		
Total		55	100,0		

the sample was almost equally distributed in a group of people, taking just the questionnaire drug (n = 29, 52,7%) , and another group taking other drugs in addition to it (n = 26, 47,3%: from one to eight).

## 2. Overview of the survey's result

The survey is far from describing systematic patterns of risk/benefit assessment. However it uncovers a series of phenomena worth of further investigation.

The descriptive analysis has given following results:<sup>591</sup>

- 1) PL reading has practically no average impact on the risk/benefit assessment. This is due both to the lack of a systematic change direction, and to the considerable proportion of no change responses in the sample. The expected frightening effect is not systematically observable: some respondents have a decreased instead of an increased risk perception after reading the PL (and the same is valid for all other parameters).
- 2) More importantly PL information seems to have absolute no impact in the decision to take the drug in this sample: *all* participants crossed the 100 score to the question asking whether the respondent was thinking of not taking the drug after reading the PL.

These data apparently contradict following results:

- 3) PL information ranking among other non-tailored sources of health information is fairly high with a mean value of 70.6 (sd 20.8, n=49, in a scale from 0 to 100) where all other sources of information (the press, the internet, mass media) are ranked significantly lower and range from a maximum of 37.4 (sd 26.3, n=43) for the internet to a minimum of 14.1 (sd 17.8, n=45) for advertisements. The reliability of the doctor as a source of information has by far the highest average score: 81.1 (sd 20.7, n=53); the pharmacist has a good second position with reliability mean score 72.7 (sd 23.6, n=52); one's own experience is valued 67 points on average (sd 24.2, n=47), whereas the opinion of friends and relatives only reaches a mean value of 34.5 (sd 22.3, n=49).
- 4) The declared value of PL information is also high: PL information is sufficient (mean = 74.8, sd 25.2, n=53) and useful (73.9, sd 26.9, n=47), not excessive (18.7, sd 28.9, n=44), a little bit disquieting (34.2, sd 31.8, n=45), but rather old (60.21, sd 30.7, n=46). However the majority of respondents do not want to have further information in the PL (mean value of desire to have further information in the PL: 40.32 in a 0-100 scale). A good 29.1% does not absolutely want any further information in the PL (0 score) and 20% are totally uncertain as to whether they desire further information in the PL (50 score). These data speak for contrasting feelings towards PL information.
- 5) More importantly, the only significant parameter change among those investigated in the paired comparisons test: the respondent's perceived level of information. This is in fact declared to be significantly higher (Z. -4.013, .000) after reading the PL: mean value 65.74 (in a 0-100 scale with sd: 27.7, n = 54) before reading the PL, and 82.12 after (sd: 20.7, n = 54).

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<sup>591</sup> Demographics data are presented in the appendix. The strength of associations has been measured through non-parametric tests: either Chi-Square for the Kruskal-Wallis Test (henceforth  $\chi^2$ ) and/or Kendall-Tau b value (henceforth  $\tau$ ). Asymptotic and approximate significance for the  $\chi^2$  and  $\tau$  value respectively will be given in brackets, e.g.: (.001).

The more reasonable hypothesis that can be advanced in order to account for 1-2 and 3-5 is that the decision settings of the participants were not sensitive to the information received in the PL.

In fact, even the systematic patterns of association between the presence of a *specific topic of concern* and some decision parameters does not result in a decision change by any of the study participants.

It seems however that, rather than by the overall amount of PL information, the reader is struck by selected items: this phenomenon has been categorized in the risk perception literature as absence of ‘spill over effect’.<sup>592</sup> The decision parameters related to this presence of a specific topic of concern are:

- 1) *Degree of confidence*. Both in the pre-PL phase,  $\tau$  -.283 (.015,  $n = 50$ ), and in the post-PL phase,  $\tau$  -.418 (.000,  $n = 52$ ), the presence of a specific topic of concern is associated with a lower degree of confidence in the therapeutic choice.
- 2) *Risk/benefit assessment*. In the post PL phase the presence of a specific topic of concern is associated with a higher risk assessment:  $\chi^2$  7.526 (.006,  $n = 48$ ).
- 3) *General benefit prognosis*. The absence of a specific topic of concern is associated with a higher general estimation of the drug benefit:  $\chi^2$  4.417 (.036,  $n = 23$ ).
- 4) *Personal benefit prognosis*. The absence of a specific topic of concern is associated with a higher estimation of the personal benefit:  $\chi^2$  4.964 (.026,  $n = 41$ ).

The presence of a specific topic of concern has an impact on the risk and benefit assessments before and after reading the PL, but not on the change patterns. This may be explained by the fact that by reading the PL some readers solve their uncertainties, some other become uncertain, and others remain as uncertain as before.

As far as the relationships between risk and benefit assessment changes and other decision parameters, general and personal assessment changes show discrepant patterns of associations as fosterer or inhibitors of change:

- i. *The level of concern* (measured by asking what would be the consequences of not taking the drug) seems to have an impact on both personal risk assessments changes: the Kruskal-Wallis test gives significant results for the personal risk prognosis change:  $\chi^2$  8,570 (.014,  $n = 30$ ), and the risk/benefit prognosis change  $\chi^2$  7,890 (.019,  $n = 44$ ).
- ii. *The level of risk acceptance* has some impact on the personal risk assessment:  $\tau$  -.333 (.012,  $n = 31$ ). The same is valid for the relationship between personal risk assessment change and *degree of confidence in choice*:  $\tau$  -.324 (.007,  $n = 33$ ). However neither the level of risk acceptance nor the degree of confidence has any influence on the other change parameters.
- iii. *Past experience* with side effects only influence the assessment change of general risk quantity:  $\tau$  .257 (.023,  $n = 34$ ); whereas past experience with benefit has some association with a positive change in risk/benefit assessment:  $\tau$  .255 (.041,  $n = 45$ ).
- iv. *Health condition* (dichotomised parameter: light disease vs. severe-chronic) has some impact on the general assessment change of risk severity:  $\tau$  -.295 (.041,  $n = 40$ ). respondents with a light disease all increase their risk assessment after

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<sup>592</sup> Viscusi, Magat, Huber, 1987: 169

- reading the PL or leave it unchanged but do not decrease it. The same is valid, but for few exceptions for the risk/benefit assessment change: respondents affected by a light disease tend to increase their risk perception after PL reading, whereas the majority of severely ill participants do not change their risk/benefit assessment:  $\tau$  -.267 (049, n = 34).
- v. Total indifference about the *perceived level of information* (50 in a range from 0 to 100) is associated with risk severity increase after reading the PL:  $\chi^2$  8,665 (.034, n = 39).
  - vi. The *PL content* has no influence on the personal risk and benefit assessment changes apart from a slight tendency of personal risk assessment decrease for PLs with numeric rather than verbal frequency descriptors:  $\tau$  -.249 (.083, n = 31). Instead the number of indefinite side effects (neither clearly light nor severe) seem to influence the assessment change of risk severity by creating a sort of shaking effect:  $\tau$  .303 (.018, n = 35) and a lower than average number side effects in general is associated with an increase in general benefit prognosis:  $\tau$  -.603 (.000, n = 19).

Topics of discussion:

- 1) Decrease in personal risk perception is influenced by the level of concern, and level of acceptance of side effects. This suggests that health risk estimation should be dealt with by drawing on prospect theory, which accounts for degree of risk aversion/proneness on the basis of the status quo and the prospect offered by the available options in relation to it (loss or gain).
- 2) The absence of an average impact is not only due to conservatism risk assessments but also by the neutralization of assessment changes in either direction. *It is however difficult to explain those cases where risk estimation not only does not change but even decreases after reading the PL.* A pragmatic explanation of this phenomenon is advanced, i.e. that the risk found in the PL is less than expected before reading it, where expectations are formed through acquaintance with the text type.
- 3) The PL content in terms of number and severity of side effects influences the benefit rather than the risk assessment change. This phenomenon can be explained by the joint influence of two distinct phenomena: the lack of clear distinction between risk and benefit in the lay assessor,<sup>593</sup> and reappraisal strategies.<sup>594</sup>

The results are presented in the following. The topics of discussion are dealt with in more detail in the qualitative part of the study and in the discussion at the end of the work. Method and demographics data are presented in the appendix.

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<sup>593</sup> Vander Stichele, 2002: 206; Alkahami, Slovic, 1994: 1090. Traditional studies on perception of technological risk at societal level have also observed that a high benefit perception obscures the perception of potential risk (which goes in the contrary direction to expert risk/benefit assessment, where high benefit should balance high risk): Slovic, et al. 1980: 149. Starr, 1969.

<sup>594</sup> See Afifi, Weiner, 2004: 181 ff.; Preuss, S: 74 ff.; Witte, 1998: 437, 438. More on this in the discussion and in the last chapter.

### 3. Descriptive statistics

#### 3.1 PL information impact

The benefit and risk assessments before and after reading the PL did not register any significant change in average. *It can be assumed that the commonly held opinion that PL information threatens the reader should be treated with more caution.* The study indeed shows that this does not invariably happen, and that instead a variety of different attitudes to this type of information leads to very different reactions. The table below shows the main descriptive statistics:

	Before PL reading			After PL reading		
	N	Mean	Std. Deviation	N	Mean	Std. Deviation
general benefit	28	66,2500	29,39592	25	71,7200	32,12284
personal benefit	37	74,4865	27,61000	41	76,9756	26,86772
severe side effects	41	28,9024	22,65260	46	39,6304	29,21671
side effects quantity	40	36,4500	24,23702	45	42,5111	25,88666
personal risk	42	41,7143	41,7143	40	39,5000	32,57654
Risk/benefit	48	20,5750	20,5750	49	24,4510	21,81802
Valid N (listwise)	15			17		

The lack of impact is also due to the neutralization effect of different directions in assessment change.

However, as the graphic shows, the number of stable assessments after reading the PL is considerable in the sample, especially for the general risk estimation (side effects quantity and severity) and the overall risk/benefit assessment. More importantly, half of the participants have not changed their degree of confidence in choice after reading the PL.

Indeed the average assessment of the degree of confidence in the therapeutic choice is rather high and it seems to be hardly shaken by reading the PL: before reading the PL, 75.46 in a 0-100 scale (sd 24.22, n = 54); after 76.69 (sd 22.98, n = 55).

The impact of PL information has been measured by carrying out Wilcoxon signed ranks tests on the same questions made before and after reading the PL. These tests have delivered following results:

**Wilcoxon Signed Ranks Test:  
Degree of confidence in choice before and after reading the PL**

	N	Mean Rank	Sum of Ranks
Negative Ranks	14(a)	12,11	169,50
Positive Ranks	13(b)	16,04	208,50
Ties	27(c)		
Total	54		

a degree of confidence in choice (POST) < degree of confidence in choice (PRE)

b degree of confidence in choice (POST) > degree of confidence in choice (PRE)

c degree of confidence in choice (POST) = degree of confidence in choice (PRE)

Degree of confidence in choice has decreased for 14 participants and increased for 13 of them. The great part has not been shaken by PL reading (27 ties). Also the impact on the overall risk/benefit assessment has been preponderantly ineffective:

**Wilcoxon Signed Ranks Test:  
Benefit/risk assessment before and after reading the PL**

	N	Mean Rank	Sum of Ranks
Negative Ranks	12(a)	12,42	149,00
Positive Ranks	10(b)	10,40	104,00
Ties	24(c)		
Total	46		

a benefit (POST) < benefit (PRE)  
b benefit (POST) > benefit (PRE)  
c benefit (POST) = benefit (PRE)

At the analytical level, changes are slightly more evident, but none of them reaches a level of statistical significance.

Focusing on the risk perception change, following percentages derive from the frequency table:

	General risk SE severity	General risk SE quantity	Personal risk
no change (ties)	36.8	41.0	30.3
more risk	42.1	35.9	<b>36.4</b>
less risk	21.1	23.1	33.3

**Table 6: Risk perception change groups: percentage.**

If we consider increase in personal risk perception, than 36.4% of the sample respondents can be said to have become more aware of the risks associated to the therapy after reading the PL. This result is in line with the AOK (WidO) findings, which reported 29% of the participants being less confident (“verunsichert”) after reading the PL.<sup>595</sup> However, as table 1 shows, PL information produced all three possible effects in the same measure (increase, decrease and no change of risk assessment).

### 3.2 Perceived level of information

The above data seem even more puzzling when considering that the only significant difference between pre and post PL phase was registered by the variable “information level”, which measured the perceived information sufficiency of participants. In a scale from 0 (no information at all) to 100 (I have no need of more information), the participants declare that their level of information reaches an average point of 82.12 after having read the PL (sd 20.77, n = 54), whereas before the mean is attested at 65.74. (sd 27.7, n = 54). The means are significantly different: Z. -4,013 (.000).

Correspondingly, ties and positive ranks are significantly more than negative ranks:

<sup>595</sup> Nink, Schröder, 2006: 76.

**Wilcoxon Signed Ranks Test:  
Perceived level of information before and after reading the PL**

	N	Mean Rank	Sum of Ranks
Negative Ranks	6(a)	11,75	70,50
Positive Ranks	29(b)	19,29	559,50
Ties	18(c)		
Total	53		

a perceived level of info: POST < perceived level of info: PRE

b perceived level of info: POST > perceived level of info: PRE

c perceived level of info: POST = perceived level of info: PRE

Therefore, participants feel that they are much more informed after reading the PL. Also the explicit evaluation of PLs after reading them is more positive than not.

### 3.3 PL evaluation

The participants were asked to make an estimate as to their opinion about several dimensions concerning PL information. The estimation means are given in the introductory overview. The estimations were clustered into three categories (rather no – uncertain – yes) as to obtain frequencies for the different levels.

#### PL evaluation

PL information: sufficient		Frequency	Percent	Valid Percent
Valid	rather no: 0 - 30	9	16,4	16,4
	uncertain: 31 - 60	15	27,3	27,3
	rather yes: 61 - 100	31	56,4	56,4
	Total	55	100,0	100,0
PL information: useful				
Valid	rather no: 0 - 30	5	9,1	10,6
	uncertain: 31 - 60	11	20,0	23,4
	rather yes: 61 - 100	31	56,4	66,0
	Total	47	85,5	100,0
Missing	System	8	14,5	
	Total	55	100,0	
PL information: old				
Valid	rather no: 0 - 30	9	16,4	19,6
	uncertain: 31 - 60	12	21,8	26,1
	rather yes: 61 - 100	25	45,5	54,3
	Total	46	83,6	100,0
Missing	System	9	16,4	
	Total	55	100,0	
PL information: excessive				
Valid	rather no: 0 - 30	33	60,0	75,0
	uncertain: 31 - 60	6	10,9	13,6
	rather yes: 61 - 100	5	9,1	11,4
	Total	44	80,0	100,0
Missing	System	11	20,0	
	Total	55	100,0	
PL information: disquieting				
Valid	rather no: 0 - 30	25	45,5	55,6
	uncertain: 31 - 60	12	21,8	26,7
	rather yes: 61 - 100	8	14,5	17,8
	Total	45	81,8	100,0
Missing	System	10	18,2	
	Total	55	100,0	

**Table 7: PL information evaluation after reading. Positive categories (sufficient, useful) have higher frequencies than negative ones (disquieting, excessive, old).**

More than half of the participants have evaluated PL information as sufficient useful and not superfluous. However, between 1/4 and 1/5 of them are “rather uncertain” about the sufficiency and usefulness estimation. Instead, uncertain judgments regarding information excessiveness have a low frequency: 10,9%.

Contrary to expectations, PL information is not declared to be disquieting by 45,5% of the participants. The same proportion of respondents considers it old. The

percentages of these last two dimensions show ambiguity towards PL information as to its threatening potential and as to its informativeness.

However the number of missing cases is significant across the parameters. In fact, whereas all participants were able to give an evaluation about sufficiency, about 14 to 21 per cent of them could not give any judgment as to the other dimensions (missing cases for each category: ‘sufficient’ = 0; ‘useful’ = 14,5%; ‘old’ = 16,4%; ‘superfluous’ = 20%; disquieting = ‘18,2%’).

The variance of attitude towards PL information can be also evinced from the frequency table regarding the desire of further information in the PL (Q. 58), where assessments are concentrated on the 0, 50, and 100 values:

**Further info in PL?**

	Frequency	Percent	Valid Percent	Cumulative Percent
Valid	,00	16	29,1	29,1
	5,00	3	5,5	34,5
	10,00	1	1,8	36,4
	15,00	1	1,8	38,2
	18,00	1	1,8	40,0
	20,00	2	3,6	43,6
	25,00	2	3,6	47,3
	40,00	1	1,8	49,1
	50,00	11	20,0	69,1
	60,00	2	3,6	72,7
	65,00	1	1,8	74,5
	70,00	2	3,6	78,2
	80,00	1	1,8	80,0
	85,00	1	1,8	81,8
	90,00	1	1,8	83,6
	100,00	9	16,4	100,0
Total		55	100,0	100,0

**Table 8: Frequency table of the expressed desire to include further information in the PL after reading it.**

By looking at the cumulative percentage, one can see that almost half of the respondents do not want any further information in the PL (0-40 = 49.1%), and a good 20% of the participants are absolute uncertain as to their desire of having further information in the PL. The mean value is 40.32 (sd, 37.36, n = 55).

### 3.4 PL ranking among other health information sources

The highest ranked health information sources are the doctor, the pharmacist, the PL, and one’s own experience. However, the sample shows a high concentration on high values for the doctor, whereas both the pharmacist and the PL have larger ranges within the upper and lower quartile – and sensibly lower mean values. All other sources of information are ranked far lower. The following table gives the main statistics:

### Information source reliability

	N	Minimum	Maximum	Mean	Std. Deviation
Doctor	53	,00	100,00	<b>81,1887</b>	20,70587
Pharmacist	52	20,00	100,00	<b>72,7308</b>	23,64037
Friends/relatives	49	,00	100,00	34,5102	22,30202
My own experience	47	5,00	100,00	67,0213	24,24198
PL	49	16,00	100,00	<b>70,6327</b>	20,87731
TV/ radio	48	,00	65,00	24,6042	20,56307
Press	49	,00	100,00	28,0816	24,45901
The internet	43	,00	90,00	37,4651	26,35594
Advertising	45	,00	50,00	14,1111	17,87866

The gap between the doctor, the pharmacist, one's own experience and PL information in relation to all other sources may indicate that the requirements of expertise and tailoredness guide the search for health information.

### 3.5 Uncertainty

Uncertainty has been measured through different parameters throughout the topic. First of all its increase/decrease in the post PL phase has been measured through the distance of benefit and risk assessments to the even estimation (.50). Secondly, it has been measured through the proportion of "I don't know" answers to the risk and benefit assessments.

Finally, it has been directly elicited both before and after reading the PL in relation to a specific topic of concern (Q. 12/45: "Is there something that makes you uncertain?").

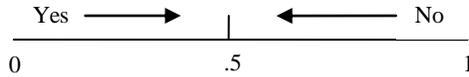
#### 3.5.1 Prognostic uncertainty, uncertainty denial, extremeness

The uncertainty represented by vagueness and fuzziness of estimation has been measured by the numbers of "I can't judge" answers, and by the tendency towards .50 judgments.

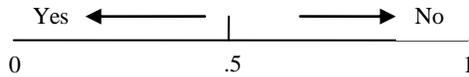
A considerable part of the sample could give no assessment either before or after reading the PL and rather opted for the "I can't judge" answer. The mean average for this answer was (2/110 = 18%) in the entire sample.

Neglecting those that give the "I can't judge answer" both before and after PL reading, one can measure the contribution of PL information in knowledge sharpening by comparing the number of cases where this option has been crossed only before but not after (mean: 7.5/55 = 13%), or only after and not before (mean: 4.1/55 = 7.4% ): this gives a ratio of 1.75: not extremely significant indeed.

The uncertainty inducing effect normally attributed to PL was also quantified by measuring the distance from the middle value (.5) before and after PL reading. This effect can be graphically described as follows. Whenever the assessment goes from values below or above .5 towards it, then it can be assumed that uncertainty relative to the parameter has increased:



On the contrary, when values tend to go towards the extreme of the scale, than the contrary hypothesis of increased judgment confidence can be entertained.



This effect was measured through the formula  $\frac{\sqrt{\sum(50-v)^2}}{N_v}$ .

Where “v” is each parameter value, and  $N_v$  the number of valid cases in the parameter. None of the variables registered a significant increase or decrease in uncertainty as can be evinced from the comparisons of the obtained results across the same questions before and after reading the PL:

	POST/PRE ratio	POST-PRE difference
General benefit	1,14	3,85
Personal benefit	1,11	3,77
Side effect severity	1,06	0,28
Side effect quantity	1,03	0,92
Personal risk	1,18	4,96
Benefit/risk odds	0,98	-0,38

**Table 9: Approach towards the .5 value or departure from it after reading the PL (measured through ratio - < 1, and difference < 0).**

No significant tendency towards uncertainty increase can be assumed along these measures.

The inclination of lay assessors to lean towards extreme judgments (0, 50, or 100) as observed in the literature on judgment elicitation,<sup>596</sup> is also present in the sample where extreme estimations have a considerable part: 0 or 100 assessments 15.84% (pre) and 16.62% (post). Also substantial is the number of complete uncertainty assessments (50): 12.98% (pre) and 12.46 (post). Non-extreme judgments made up 71.16% of responses before and 70.64% after PL reading.

### 3.5.2 Specific topics of concern generating uncertainty

Respondents who expressed uncertainty about a topic of concern are 18 out of 55 before reading the PL and 22 afterwards. However a “two x two” contingency table

<sup>596</sup> See Slovic, 2000: 109, 222. Highly sophisticated elicitation techniques have been especially devised to counteract this tendency, which however could not be used in the context of a survey. See: Edwards, von Winterfeldt, 1986: 116 ff. ; Yates, 1990: 16 ff. The tendency to extreme assessment is part of the judgment overconfidence phenomenon first analyzed by Oskamp (1965) and further investigated a. o. by Fischhoff, Slovic, Lichtenstein, 1977.

shows that PL information has also removed the uncertainty in some case (5), and raised doubts in other cases (9), where previously no uncertainty affected the subject.

PRE	POST		
	No uncertainty	Uncertainty	
No uncertainty	28	9	34
Uncertainty	5	13	18
	30	22	52
Missing: 3			55

Topics of concern more often address specific items of information than side effects in general.<sup>597</sup>

In many cases, reading the PL does not remove it, but rather adds other uncertainties (see cases 2, 9, 10, 34, 35, 41, 44). In other cases the uncertainty before reading the PL is less worrying than after reading it (13, 27). At any rate, in general, *topics of concern seem to be more focused and specific in the post PL phase* (see: 12, 32, 50). Apprehensions are rather vague and indeterminate before reading the PL, whereas they become rather focused and pressing afterwards.

In five cases the worries expressed before reading the PL have been removed afterwards.

### 3.5.2.1 Impact of the specific topics of concern on decision parameters

The presence of a specific topic of concern is related to the degree of confidence in choice both before,  $\chi^2 5.127$  (.024, n = 50) and after reading the PL,  $\chi^2 11.661$  (.001, n = 52) seems to be influenced by the presence of a specific topic of concern.

The Kruskal-Wallis test is confirmed also by symmetric measures of correlation and  $\chi^2$  tests:

Chi-Square Tests				Symmetric Measures					
	Value	df	Asy mp. Sig. (2-sided)		Value	Asy mp. Std. Error <sup>b</sup>	Approx. <sup>†</sup>	Approx. Sig.	
Pearson Chi-Square	22,080 <sup>a</sup>	12	,037	Ordinal by Ordinal	Kendall's tau-b	-,283	,113	-2,431	,015
Continuity Correction					Kendall's tau-c	-,342	,141	-2,431	,015
Likelihood Ratio	25,288	12	,014		Spearman Correlation	-,323	,130	-2,368	,022 <sup>c</sup>
Linear-by-Linear Association	4,041	1	,044	Interval by Interval	Pearson's R	-,287	,139	-2,077	,043 <sup>c</sup>
N of Valid Cases	50				N of Valid Cases	50			

a. 23 cells (88,5%) have expected count less than 5. The minimum expected count is ,32.

b. Not assuming the null hypothesis.

c. Using the asymptotic standard error assuming the null hypothesis.

†. Based on normal approximation.

<sup>597</sup> Tables with the transcription of the specific topics of concern are presented in the appendix.

Chi-Square Tests				Symmetric Measures					
	Value	df	Asy mp. Sig. (2-sided)			Value	Asy mp. Std. Error <sup>b</sup>	Approx. †	Approx. Sig.
Pearson Chi-Square	23,399 <sup>a</sup>	13	,037	Ordinal by Ordinal	Kendall's tau-b	-,418	,103	-3,966	,000
Continuity Correction					Kendall's tau-c	-,534	,135	-3,966	,000
Likelihood Ratio	29,445	13	,006		Spearman Correlation	-,478	,118	-3,850	,000 <sup>c</sup>
Linear-by-Linear Association	13,434	1	,000	Interval by Interval	Pearson's R	-,513	,110	-4,229	,000 <sup>c</sup>
N of Valid Cases	52								

a. 25 cells (89,3%) have expected count less than 5. The minimum expected count is ,42.

a. Not assuming the null hypothesis.  
b. Using the asymptotic standard error assuming the null hypothesis.  
c. Based on normal approximation.

**Table 10: Measures of correlation between the presence of a specific topic of concern and the degree of confidence (in the previous page: before reading the PL; above: after reading the PL).**

As for the analytical benefit and risk assessments, the presence of a topic of concern generating uncertainty does not impact them in the pre PL phase, apart from the personal benefit assessment where the mean rank between the two groups uncertainty/no uncertainty is respectively 13,29 and 20,46 which means that the prognosis of personal benefit is significantly higher for participants who perceive no uncertainty:  $\chi^2$  4,073 (.044, n 35).

In the post PL phase the presence of a specific topic of uncertainty has a strong impact on the benefit prognosis both general:  $\chi^2$  4.417 (.036, n = 23) and personal:  $\chi^2$  4.964 (.026, n = 43), as well as on the overall risk/benefit assessment:  $\chi^2$  7.526 (.006, n = 48).

These results can be interpreted as an indirect confirmation, that specific topics of uncertainty arising from the PL text (uncertainty POST) have a higher capability of affecting the risk/benefit assessment than vague uncertainties (uncertainty PRE) deriving from perceived domain incompetence. However, oddly enough, correlation coefficients with risk perception dimensions are not significant. *It seems that rather than influencing the risk perception, the presence of uncertainty about a specific topic tends to have a downplaying effect on the benefit assessment.* This phenomenon is recurrent all along this study.<sup>598</sup>

Interestingly, the presence of a specific topic of concern is also related to the reliability level assigned to the doctor as an information source. This is not only valid for the presence of a topic of concern before reading the PL, but also afterwards. The following tables present the significance measures for the association between the presence of a specific topic of concern and the reliability score assigned to the doctor before (above) and after (below) PL reading:

<sup>598</sup> For discussion see next paragraph and following chapter.

Chi-Square Tests			
	Value	df	Asy mp. Sig. (2-sided)
Pearson Chi-Square	8,585 <sup>a</sup>	3	,035
Continuity Correction			
Likelihood Ratio	8,395	3	,039
Linear-by-Linear Association	7,579	1	,006
N of Valid Cases	49		

a. 5 cells (62,5%) have expected count less than 5. The minimum expected count is 1,53.

Symmetric Measures					
		Value	Asy mp. Std. Error <sup>b</sup>	Approx. <sup>†</sup>	Approx. Sig.
Ordinal by Ordinal	Kendall's tau-b	-,373	,125	-2,822	,005
	Kendall's tau-c	-,387	,137	-2,822	,005
	Spearman Correlation	-,398	,133	-2,973	,005 <sup>c</sup>
Interval by Interv:	Pearson's R	-,397	,137	-2,969	,005 <sup>c</sup>
N of Valid Cases		49			

a. Not assuming the null hypothesis.

b. Using the asymptotic standard error assuming the null hypothesis.

c. Based on normal approximation.

**Table 6: Measures of correlation between the presence of a specific topic of concern and doctor's reliability (above: before reading the PL; on the right, after reading the PL).**

People perceiving no special topic of uncertainty are more likely to have a higher reliability in the doctor. The direction of the relationship cannot be derived from these data though.

In the post PL phase an additional question has been asked in order to assess whether therapy incept would be conditioned on the acquisition of further information: Q. 49: "Would you look for further information before keeping on with the therapy?". Also this parameter has been found to be positively related to perceived uncertainty about a specific topic. A very strong intention to further enquire before keeping on with the therapy is equally likely to be associated with both the presence and the absence of a specific topic of concern. But low and absolute no desire to further enquire is predominantly associated with the absence of a specific topic of concern:

Symmetric Measures					
		Value	Asy mp. Std. Error <sup>b</sup>	Approx. <sup>†</sup>	Approx. Sig.
Ordinal by Ordinal	Kendall's tau-b	,244	,119	2,044	,041
	Kendall's tau-c	,308	,150	2,044	,041
	Spearman Correlation	,277	,135	2,019	,049 <sup>c</sup>
Interval by Interv:	Pearson's R	,309	,134	2,272	,028 <sup>c</sup>
N of Valid Cases		51			

a. Not assuming the null hypothesis.

b. Using the asymptotic standard error assuming the null hypothesis.

c. Based on normal approximation.

**Table 7: Measures of correlation between the presence of a specific topic of concern and the desire to further enquire about the drug.**

Similar considerations hold for the correlation between the perception of uncertainty about a specific topic of concern and *further desire to enquire the doctor again*:

Chi-Square Tests				Symmetric Measures			
	Value	df	Asy mp. Sig. (2-sided)		Value	Asy mp. Std. Error <sup>b</sup>	Approx. <sup>†</sup> Approx. Sig.
Pearson Chi-Square	27,426 <sup>a</sup>	10	,002	Ordinal by Ordinal	Kendall's tau-b	,500	,105 4,673 ,000
Continuity Correction					Kendall's tau-c	,605	,129 4,673 ,000
Likelihood Ratio	34,165	10	,000		Spearman Correlation	,555	,117 4,478 ,000 <sup>c</sup>
Linear-by-Linear Association	15,999	1	,000	Interval by Interval	Pearson's R	,590	,113 4,899 ,000 <sup>c</sup>
N of Valid Cases	47			N of Valid Cases		47	

a. 19 cells (86,4%) have expected count less than 5. The minimum expected count is ,45.

b. Not assuming the null hypothesis.

c. Using the asymptotic standard error assuming the null hypothesis.

† Based on normal approximation.

**Table 8: Measures of correlation between the presence of a specific topic of concern and the desire to further enquire about the drug.**

The relationship is mostly due to the different distribution of the no-uncertainty assessments in the two extreme points of expressed desire to further enquire the doctor. This finding can be explained by the fact that the emergence or persistence of uncertainty *after* having read the PL, might be associated, with a certain *trust loss* in the physician at least for a portion of the sample.

#### 4. Decision dimensions and PL impact

Because the average PL impact did not show any significant trend, the assessments parameters have been investigated along dimensions relating to the therapeutic decision, in order to identify factors hindering or fostering change in risk and benefit assessment:

PL	PL content; Declared PL value; Information reliability.
Decision model: Decision/information dimensions:	Degree of participation in decision making Level of concern (motivation in undertaking therapy), health condition; confidence in choice; information relevance to decision; information promise; perceived level of information; risk acceptance.
Prior knowledge:	chronic vs. acute therapy; experience with drugs efficacy and side effects.

The change has been measured both including the direction dimension and in absolute terms (absolute amount of change irrespective of the direction).

##### 4.1 PL information design

The first parameter under investigation has been the package leaflet itself. The parameters investigated are number of light side effects, number of “indefinite” side

effects, number of severe side effects, total number of side effects, and the indication of numeric frequency for side effects.<sup>599</sup>

The only content variable affecting personal risk perception seems to be the numeric indication of side effects frequencies.

Lower than average numbers of light side effects shows a tendency to be associated with a decrease in risk perception quantity. “Indefinite” side effects rather have a “shaking” effect, precisely because of the non interpretability of their importance. The lower than average total number of side effects also shows the tendency to be associated with increased benefit.

In general, the results that emerge from the investigation of general and personal assessments in relation to the PL content show that pragmatic considerations linked to text interpretation should be considered in the analysis of PL information effect. Expectations about the text type and hypotheses about its function might guide the reader in gauging the drug risk and benefit associated to the drug.

#### **4.1.1 Number of light side effects**

The number of light side effects shows only a tendency to influence the risk prognosis change, and among the different risk assessments, only the prognosis regarding the quantity of side effects: Pearson’s  $r$  .299 (.068,  $n = 38$ ). Personal risk prognosis and severity of side effects instead are not changed by the number of light side effects.

The association however is due to an interesting phenomenon, which has been observed also in the variables “number of severe side effects” and “number of indefinite side effects”: the less than average amount of side effects, not only contribute to inhibit increase in risk perception, but seems to be associated with decrease.

#### **4.1.2 Number of indefinite side effects**

Non-parametric tests give no significance coefficient for the parameter measuring the number of indefinite side effects and risk or benefit change.

The impact of indefinite side effects is however significant when measured in absolute terms. The group with higher amount of indefinite side effects is associated with greater change in the parameter risk severity (irrespective of the direction):

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<sup>599</sup> Methods for PL classification are presented in the appendix.

Symmetric Measures					
		Value	Asymp. Std. Error <sup>a</sup>	Approx. †	Approx. Sig.
Ordinal by Ordinal	Kendall's tau-b	,303	,127	2,356	,018
	Kendall's tau-c	,305	,129	2,356	,018
	Spearman Correlation	,356	,152	2,191	,036 <sup>c</sup>
Interval by Interv:	Pearson's R	,374	,127	2,317	,027 <sup>c</sup>
N of Valid Cases		35			

a. Not assuming the null hypothesis.

b. Using the asymptotic standard error assuming the null hypothesis.

c. Based on normal approximation.

**Table 9: Measures of correlation between the number of indefinite side effects and risk severity assessment change.**

This could mean that indefinite side effects have a “shaking effect”, in that they can both contribute to decrease and to increase the risk severity perception. As accounted for in the PL classification, indefinite side effects can be over- and underestimated as well.

Pragmatic aspects of text interpretation help explain this phenomenon. It might in fact be assumed that, when confronted with a PL text, the average reader has implicit expectations about its content and form: it can happen that the reader interprets the indefinite side effects in the PL at hand as less or more dangerous than subjectively expected, and therefore perceives the drug as less or more threatening than expected before reading the PL. However further investigations are required in order to consolidate these conjectures.

#### 4.1.3 Number of severe side effects

The amount of definitely severe side effects seems to have no precise impact pattern on risk perception change. This could also be explained by pragmatic factors: it can be assumed that people presume to learn about the eventuality of severe side effects from the doctor, so that whenever the reader encounters side effects, which he does not know of but that are undoubtedly severe, he reasons that he is unlikely to be concerned by them, because otherwise the doctor would have mentioned them (more on this in the qualitative analysis, next chapter).

#### 4.1.4 Total number of side effects

The variable measuring the total number of side effects confirms the associations found for the variable “light side effects”: change in risk quantity perception:  $\tau$  .278 (.012,  $n = 38$ ) and for the variable “indefinite side effects”: absolute change in risk severity perception:  $\tau$  .234 (.068,  $n = 39$ ).

However the significance levels of the relationship with the absolute change in risk severity perception is lower than for the number of indefinite side-effects, which could strengthen the hypothesis, that more than the overall number of side effects, *their ambiguity and vagueness (indefinite side effects) are the major responsible for risk severity perception change.*

The highest significance level of correlation between assessment change and amount of total side effects is to be found in the parameter general benefit:

Symmetric Measures					
		Value	Asymp. Std. Error <sup>a</sup>	Approx. <sup>†</sup>	Approx. Sig.
Ordinal by Ordinal	Kendall's tau-b	-,603	,109	-5,136	,000
	Kendall's tau-c	-,673	,131	-5,136	,000
	Spearman Correlation	-,714	,112	-4,210	,001 <sup>c</sup>
Interval by Interv:	Pearson's R	-,698	,095	-4,018	,001 <sup>c</sup>
N of Valid Cases		19			

a. Not assuming the null hypothesis.  
b. Using the asymptotic standard error assuming the null hypothesis.  
c. Based on normal approximation.

**Table 10: Measures of correlation between the total number of side effects and general benefit assessment change.**

This datum strengthens the hypothesis that the source of potential benefit and risk is seen in its overall effect with no clear-cut distinction between the two parameters, and that when forced to assess the parameters separately, subjects tend to adjust their level of perceived benefit, rather than changing the perception of risk potential.

The most remarkable datum however, is that no correlation has been found between number of side effects, whether light, indefinite or severe and change in *personal* benefit and risk prognosis. In this sense a gap opens between the objective perception of the damaging and beneficial potentialities associated with the drug in general, and the expected personal efficacy and risk.

In addition to the findings related to uncertainty perception, this is a further confirmation, that personal risk and benefit perception is affected by specific topics of concern, which are deemed personally relevant by the subject, rather than being influenced by the overall risk message.

In the qualitative part of this work the rationale of this distinction will be further investigated.

#### 4.1.5 Numeric frequency indicators

The indication of the numeric frequency of side effects seems to be one of the few variables linked to *personal* risk perception change: precisely, numerical frequency indicators tend to be associated to a decrease in personal risk perception. The ordinal tests only point to a tendency:  $\tau$  -.249 (.083,  $n = 31$ ). However, the t-test for dependent groups also suggests a trend worth of consideration: correlation coefficient: -.330 (.069  $n = 31$ ). The means difference between the two groups is: 2,2632 average increase for the group “no numerical frequency” and -15,2500 average decrease for the group “numerical frequencies”.

Given the low percentages generally associated to side effects in the PL list, this can be cautiously interpreted as a sign of Bayesian integration of probabilistic information into a personal prognosis.

## 4.2 Declared PL value

Also the dimensions related to PL information evaluation (sufficient, old, excessive, disquieting, and useful), are rather associated to *general* risk and benefit perception change than to *personal* risk and benefit assessment change.

1. The parameter “*sufficiency*” has a significant relationship with positive changes in *degree of confidence*:  $\chi^2$  6,315 (.043, n = 52).
2. The perception of PL information as *disquieting* is associated to change in *general benefit*:  $\chi^2$  5,765 (.056, n = 16) and *general risk (SE severity)* perception:  $\chi^2$  6,713, (.035, n = 32).
3. The Kruskal Wallis test gives no other significant associations among assessment changes and PL evaluation categories. However symmetric measures of correlation indicate a correlation between the perception of PL information *usefulness* and increase in general benefit perception:  $\tau$  .447 (.01, n = 17).

## 4.3 Information source reliability

As already illustrated in paragraph 2, PL reliability ranks fairly high within the other sources of pharmaceutical information. However, the expected relationship between high reliability in the PL and impact in risk/benefit perception has not been observed. Instead an association has been found between the perceived reliability of the doctor and the change in general risk assessment quantity:  $\chi^2$  7,607 (.055, n = 37); and between one’s own experience as a source of information and the change in the risk/benefit assessment:  $\chi^2$  6,678 (.035, n = 40).

In general, deeper research is needed for analyzing drug consumer’s change in risk perception through different, eventually conflicting, information sources.

## 4.4 Perceived relevance of further information to decision

The correlation of assessment changes and decision dimensions is all but systematic and consistent. The questions measuring decision dimensions are the following:

1. Level of concern  
Q. 9: “What would happen, if you do not take the drug?”
2. Degree of confidence in decision  
Q. 10/40: “Are you satisfied with the treatment choice?”
3. Perceived level of information  
Q. 11/44: “How much information do you have about the treatment?”
4. Relevance of missing information to the decision  
Q. 15/48: “Are you considering not to take the treatment because of eventual missing information?”
5. Promise (estimated potential to remove the uncertainty)  
Q. 14/47: “Could an eventual clarification about it [topic of uncertainty] eliminate the uncertainty?”
6. Acceptance of side effects  
Q. 21: “You must take side effects into account, when you take a drug” (0 to 100 assessment).
7. Experience with drug  
Q. 18: “How much experience do you have with drugs?”

- Q. 19: “In my case drugs are effective ... (from 0 = never to 100 = always)”  
 Q. 21: “I had side effects in the past, when I took drugs ... (from 0 = never to 100 = always)”;  
 Q. 20: “When I am ill, it is difficult for me to distinguish between side effects and illness symptoms”.

#### 4.5 Level of concern

Level of concern has not been elicited directly on a continuous scale but derived from the responses to a counterfactual question (Q. 9): “What would be the consequence of not taking the treatment?”. The possible answers ranged from “I should stay home for a couple of day” (which was assigned low level of concern) to the necessity of a surgical operation (high level of concern). In-between, the possibility of worsening and complications was contemplated (medium level). The answers battery allowed also for a personal response (assigned to one of the three categories depending on the content) and for the “I don’t know option”, which nobody crossed.

Descriptive statistics are given below:

level of concern					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	low	11	20,0	21,6	21,6
	medium	33	60,0	64,7	86,3
	high	7	12,7	13,7	100,0
	Total	51	92,7	100,0	
Missing	System	4	7,3		
Total		55	100,0		

The level of concern is one of the few parameters which seem to show a significant correlation with change in personal assessments.

The Kruskal-Wallis test gives significant results for the personal risk prognosis change:  $\chi^2 8,570$  (.014, n = 30) and for the risk benefit assessment change:  $\chi^2 7,890$  (.019, n = 44).

Change in risk/benefit assessment seems to undergo an increase in risk perception for low concerned participants and to show the opposite tendency for high concerned ones. This can be read within the framework of prospect theory<sup>600</sup> as the result of different initial choice outlets: *low concerned consumers will tend to risk aversion and therefore perceive the drug risk as higher than the inconveniences brought about by their illness, instead people with severe diseases will tend to be risk prone and therefore have higher tolerance for the drug risk read in the PL.*

Yet, the decrease in risk perception after reading the PL can only be explained if readers are also assumed to have expected more risk than found in the PL. This can only be investigated within the framework of expectations related to the text type.

<sup>600</sup> Kahneman, Tversky (1979); Tversky, Kahnemann (1992). The survey was not designed to investigate the data in this respect though and therefore deeper analysis of this phenomenon is not allowed by the findings. Also the discussion in chapter 9 will not consider prospect theory in the analysis of PL information processing, because this theory rather addresses the decision maker’s risk attitude, whereas the final chapter deals with his degree of processing accuracy as a function of the expected value of PL information.

## 4.6 Health condition

An indirect measure of the level of concern is also the health condition. This parameter has been investigated as a dichotomic variable: light vs. severe-chronic disease.

Illness severity seems to be associated with the overall risk/benefit assessment and risk severity, but only loosely associated with the assessment change in risk quantity. Patterns are similar to those seen in the level of concern: risk increase in the risk/benefit assessment is more frequent in participants affected by a light disease:

Symmetric Measures					
		Value	Asy mp. Std. Error <sup>a</sup>	Approx. <sup>†</sup>	Approx. Sig.
Ordinal by	Kendall's tau-b	-,295	,137	-2,039	,041
Ordinal	Kendall's tau-c	-,320	,157	-2,039	,041
	Spearman Correlation	-,327	,153	-2,135	,039 <sup>c</sup>
Interval by Interv:	Pearson's R	-,328	,149	-2,137	,039 <sup>c</sup>
N of Valid Cases		40			

a. Not assuming the null hypothesis.

b. Using the asymptotic standard error assuming the null hypothesis.

c. Based on normal approximation.

**Table 11: Measures of correlation between health condition and risk/benefit assessment change.**

Also the increase of risk severity is more frequent in respondents affected by a light disease:

Symmetric Measures					
		Value	Asy mp. Std. Error <sup>a</sup>	Approx. <sup>†</sup>	Approx. Sig.
Ordinal by	Kendall's tau-b	-,267	,129	-1,965	,049
Ordinal	Kendall's tau-c	-,315	,160	-1,965	,049
	Spearman Correlation	-,303	,148	-1,796	,082 <sup>c</sup>
Interval by Interv:	Pearson's R	-,335	,155	-2,009	,053 <sup>c</sup>
N of Valid Cases		34			

a. Not assuming the null hypothesis.

b. Using the asymptotic standard error assuming the null hypothesis.

c. Based on normal approximation.

**Table 12: Measures of correlation between health condition and risk severity assessment change.**

Participants affected by light diseases more probable than not adjust their risk assessment in a positive direction. This pattern however is not observed for change in *personal* risk assessment.

## 4.7 Degree of confidence in choice

The degree of confidence in choice is relatively high in the sample: there is however also a consistent part of totally uncertain respondents (50 score: 16,7%, n = 9). Main statistics are given in the tables:

**Statistics**

degree of confidence in choice		
N	Valid	54
	Missing	1
Mean		75,4630
Median		75,0000
Mode		100,00
Std. Deviation		24,24849
Minimum		,00
Maximum		100,00

degree of confidence in choice					
	Frequency	Percent	Valid Percent	Cumulative	
				Percent	
Valid	,00	1	1,8	1,9	1,9
	25,00	1	1,8	1,9	3,7
	30,00	2	3,6	3,7	7,4
	40,00	1	1,8	1,9	9,3
	50,00	9	16,4	16,7	25,9
	60,00	1	1,8	1,9	27,8
	70,00	3	5,5	5,6	33,3
	75,00	10	18,2	18,5	51,9
	80,00	2	3,6	3,7	55,6
	85,00	1	1,8	1,9	57,4
	90,00	5	9,1	9,3	66,7
	95,00	3	5,5	5,6	72,2
	100,00	15	27,3	27,8	100,0
Total		54	98,2	100,0	
Missing	System	1	1,8		
Total		55	100,0		

The degree of confidence in choice seems to be correlated to personal risk perception change: respondents with low degree of confidence or rather uncertain about the therapeutic choice are more frequently associated with personal risk increase. Participants declaring high or very high confidence in their choice tend to either leave their personal risk assessment unchanged or to decrease it after PL reading. Below the table gives the level of significance of this association:

Symmetric Measures					
		Value	Asymp. Std. Error <sup>a</sup>	Approx. <sup>b</sup>	Approx. Sig.
Ordinal by Ordinal	Kendall's tau-b	-,324	,117	-2,702	,007
	Kendall's tau-c	-,335	,124	-2,702	,007
	Spearman Correlation	-,415	,142	-2,538	,016 <sup>c</sup>
Interval by Interv:	Pearson's R	-,329	,128	-1,939	,062 <sup>c</sup>
N of Valid Cases		33			

a. Not assuming the null hypothesis.

b. Using the asymptotic standard error assuming the null hypothesis.

c. Based on normal approximation.

**Table 13: Measures of correlation between degree of confidence in choice and personal risk assessment change.**

This data might suggest that PL information impact tends to be biased by a high degree of confidence in decision. In fact, a decrease in risk estimation is hardly understandable as the sole product of PL reading. The fact that high degree of confidence contributes to no change or decreased risk perception suggests that it predisposes the reader towards an optimistic bias (similarly to the high degree of

confidence in the doctor). This phenomenon can be traced back to strategies against cognitive dissonance, which have been already observed in the literature devoted to health risk information processing.<sup>601</sup>

However, no corresponding association has been founded between the degree of confidence in choice and the change in *personal* benefit perception.

#### 4.8 Perceived level of information before reading the PL

Main statistics and the frequency distribution of the variable measuring perceived level of information are presented below:

Statistics			'perceived level of information'				
perceived level of information			Frequency	Percent	Valid Percent	Cumulative Percent	
N	Valid	54	Valid	,00	1	1,8	1,9
	Missing	1	5,00	1	1,8	1,9	3,7
Mean		65,7407	10,00	1	1,8	1,9	5,6
Median		60,0000	25,00	1	1,8	1,9	7,4
Mode		50,00	30,00	3	5,5	5,6	13,0
Std. Deviation		27,70136	50,00	19	34,5	35,2	48,1
Minimum		,00	55,00	1	1,8	1,9	50,0
Maximum		100,00	65,00	1	1,8	1,9	51,9
			70,00	5	9,1	9,3	61,1
			80,00	2	3,6	3,7	64,8
			85,00	1	1,8	1,9	66,7
			90,00	2	3,6	3,7	70,4
			95,00	5	9,1	9,3	79,6
			100,00	11	20,0	20,4	100,0
			Total	54	98,2	100,0	
	Missing System		Missing System	1	1,8		
			Total	55	100,0		

The perceived level of information is associated to the change in risk severity prognosis:  $\chi^2 8,665$  (.034, n = 39).

Interestingly, the mean ranks show that increase in risk severity perception is mostly associated to *total uncertainty about the perceived level of information before reading the PL*:

	perceived level of information	N	Mean Rank
general risk prognosis	0-> 49	4	17,75
(SE severity): change	<b>50</b>	<b>12</b>	<b>27,08</b>
	51 -> 89	8	12,94
	90 -> 100	15	18,70
	Total	39	

Whereas all but one respondent in the total uncertain group (50) have increased or maintained the prior level of SE severity perception, participants with high information level awareness before reading the PL are rather associated with stable or

<sup>601</sup> Steckelberg, 2004b, 2005.

decreased SE severity. Very high and very low perception of information level is not neatly associated with any specific pattern.

#### 4.9 Information relevance and promise

No correlation at all has been found between assessments change and the variable related to the perceived relevance of further information to decision (Q.15). Neither has it been found for the variable eliciting the perceived information promise (Q.14).

#### 4.10 Risk acceptance

The following tables give the main statistics for the parameter measuring the level of risk acceptance in the questionnaire's respondents: Q. 21 "You need to take side-effects into account when you take a drug".

Statistics			acceptance of side effects				
acceptance of side effects			Frequency	Percent	Valid Percent	Cumulative Percent	
N	Valid	52	Valid	.00	3	5,5	5,8
	Missing	3	5,00	3	5,5	5,8	11,5
Mean		58,7500	10,00	1	1,8	1,9	13,5
Median		60,0000	15,00	1	1,8	1,9	15,4
Mode		50,00	20,00	1	1,8	1,9	17,3
Std. Deviation		32,40181	25,00	2	3,6	3,8	21,2
Minimum		,00	30,00	1	1,8	1,9	23,1
Maximum		100,00	35,00	1	1,8	1,9	25,0
			40,00	1	1,8	1,9	26,9
			50,00	10	18,2	19,2	46,2
			55,00	1	1,8	1,9	48,1
			60,00	4	7,3	7,7	55,8
			65,00	2	3,6	3,8	59,6
			70,00	1	1,8	1,9	61,5
			75,00	1	1,8	1,9	63,5
			80,00	3	5,5	5,8	69,2
			90,00	6	10,9	11,5	80,8
			95,00	2	3,6	3,8	84,6
			100,00	8	14,5	15,4	100,0
			Total	52	94,5	100,0	
	Missing System	3	Missing System	3	5,5		
			Total	55	100,0		

The parameter risk acceptance seems to be related to the *personal* risk assessment change. The symmetric measures of non-parametric tests give rather high significance levels:

Symmetric Measures					
		Value	Asymp. Std. Error <sup>a</sup>	Approx. $\tau$ <sup>b</sup>	Approx. Sig.
Ordinal by Ordinal	Kendall's tau-b	-,333	,127	-2,513	,012
	Kendall's tau-c	-,343	,137	-2,513	,012
	Spearman Correlation	-,400	,148	-2,348	,026 <sup>c</sup>
Interval by Interval	Pearson's R	-,424	,118	-2,521	,017 <sup>c</sup>
N of Valid Cases		31			

a. Not assuming the null hypothesis.

b. Using the asymptotic standard error assuming the null hypothesis.

c. Based on normal approximation.

**Table 14: Measures of correlation between acceptance of side effects and personal risk assessment change.**

Whereas participants with high risk acceptance distribute over the entire range, respondents with low risk acceptance tend to increase their risk perception after having read the PL. Respondents who are uncertain as to their readiness to accept side effects show an intermediate pattern between the two.

#### 4.11 Experience with drugs

Experience has been elicited in relation to drugs in general and to drug side effects and benefits in particular.

Descriptive statistics about the variables are given below:

Statistics				
		past experience with drug	past experience with drug: benefits	experience with side effects
N	Valid	54	53	45
	Missing	1	2	10
Mean		59,5741	74,3774	43,9778
Median		50,0000	75,0000	50,0000
Mode		50,00	75,00 <sup>a</sup>	50,00
Std. Deviation		28,33066	17,58411	26,91273
Minimum		,00	15,00	,00
Maximum		100,00	100,00	100,00

a. Multiple modes exist. The smallest value is shown

No significant correlation between experience in general and change in risk or benefit assessment has been observed.

A significant association has instead been found between positive experience with drug benefits and risk/benefit odds change  $\tau$  .255 (.041,  $n = 45$ ).

Experience with side effects seems to have some influence only on the general risk prognosis about risk quantity:

Symmetric Measures					
		Value	Asymp. Std. Error <sup>a</sup>	Approx. <sup>b</sup>	Approx. Sig.
Ordinal by Ordinal	Kendall's tau-b	,257	,111	2,271	,023
	Kendall's tau-c	,258	,114	2,271	,023
	Spearman Correlation	,327	,135	1,957	,059 <sup>c</sup>
Interval by Interval	Pearson's R	,275	,130	1,619	,115 <sup>c</sup>
N of Valid Cases		34			

a. Not assuming the null hypothesis.

b. Using the asymptotic standard error assuming the null hypothesis.

c. Based on normal approximation.

**Table 15: Measures of correlation between past experience with side effects and risk quantity assessment change.**

Subjects who declared to have had side effects more often than not in the past either do not change their personal risk assessment or they increase it. The contrary holds for people with low experience with side effects. Totally uncertain subject (those who assess a 50 judgment) as well as respondents declaring low experience with side effects distribute over the entire range.

The questions related to prior experience were devised in order to assess consumer's bayesianism. However no patterns of correlation have been found between risk and benefit assessments and past experience about drug benefits and risks. *This is puzzling but could be explained by the hypothesis that drug users rather stick to the risk/benefit assessment delivered by the doctor as for the personal benefit and risk prognosis.*

#### 4.12 Participation in decision

Participation in decision has been measured through a multiple response question:

Q. 17: "How was the treatment chosen?"

- a) My physician has prescribed it to me.
- b) My physician recommended it to me and I accepted the proposal.
- c) After reflecting together with the physician, it turned out that this is the most effective treatment for me.
- d) After reflecting together with the physician, it turned out that with this treatment I will have the least possible adverse reactions.
- e) There's no alternative.
- f) I don't know of any alternative.
- g) Other.

The responses have been given a score depending on their content: a = 0; b = 1; c = 2, d = 2, e = 1, f = -1. The total sum for each case has been considered as the value of a new variable measuring the level of participation in the therapeutic decision.

The variable "choice participation" shows no important correlation with the change variables apart from a significant value for the association with change in risk quantity assessment:

Symmetric Measures					
		Value	Asymp. Std. Error <sup>a</sup>	Approx. <sup>b</sup>	Approx. Sig.
Ordinal by	Kendall's tau-b	-,273	,111	-2,404	,016
Ordinal	Kendall's tau-c	-,248	,103	-2,404	,016
	Spearman Correlation	-,341	,136	-2,179	,036 <sup>c</sup>
Interval by Interv:	Pearson's R	-,319	,135	-2,019	,051 <sup>c</sup>
N of Valid Cases		38			

a. Not assuming the null hypothesis.

b. Using the asymptotic standard error assuming the null hypothesis.

c. Based on normal approximation.

**Table 15: Measures of correlation between level of participation in decision and risk quantity assessment change.**

Analogously to the effect of high degree of confidence on the personal risk assessment change, higher participation in the choice is associated with side effects quantity decrease.

## 5. Interrelations among decision parameters

Because decision parameters seemed to have unsystematic influence over risk and benefit assessment change, their reciprocal interrelation has been investigated in order to check if they captured the dynamics related to information seeking behavior in a decision under uncertainty.

As far as experience is concerned, a significant relationship as been observed between therapy type (chronic vs. acute) and perceived level of information:

Symmetric Measures					
		Value	Asymp. Std. Error <sup>a</sup>	Approx. <sup>b</sup>	Approx. Sig.
Ordinal by	Kendall's tau-b	,347	,106	3,272	,001
Ordinal	Kendall's tau-c	,439	,134	3,272	,001
	Spearman Correlation	,393	,119	3,084	,003 <sup>c</sup>
Interval by Interv:	Pearson's R	,370	,124	2,876	,006 <sup>c</sup>
N of Valid Cases		54			

a. Not assuming the null hypothesis.

b. Using the asymptotic standard error assuming the null hypothesis.

c. Based on normal approximation.

**Table 16: Measures of correlation between therapy type (acute vs. severe/chronic) and perceived level of information (before PL reading).**

Chronic cases are associated with higher perceived level of information. Furthermore, as predicted by the Bayesian model, degree of confidence in choice is associated to the perceived level of information: The table gives the tests results:

Symmetric Measures					
		Value	Asymp. Std. Error <sup>a</sup>	Approx. T <sup>b</sup>	Approx. Sig.
Ordinal by Ordinal	Kendall's tau-b	,261	,114	2,270	,023
	Kendall's tau-c	,259	,114	2,270	,023
	Spearman Correlation	,307	,134	2,300	,026 <sup>c</sup>
Interval by Interval	Pearson's R	,290	,129	2,163	,035 <sup>c</sup>
N of Valid Cases		53			

a. Not assuming the null hypothesis.

b. Using the asymptotic standard error assuming the null hypothesis.

c. Based on normal approximation.

**Table 17: Measures of correlation between degree of confidence in choice and perceived level of information (before PL reading).**

High and very high degree of confidence in the choice is associated with high and very high perceived level of knowledge, whereas the level of information of uncertain participants spreads all over the distribution range, and respondents with low confidence in the decision are distributed in the 25-30 level of information slot. Perceived relevance of missing information is also related to degree of confidence in decision. Subjects perceiving a high importance of missing information for the decision are extremely unlikely to have a high degree of confidence in the decision:

Symmetric Measures					
		Value	Asymp. Std. Error(a)	Approx. T(b)	Approx. Sig.
Ordinal by Ordinal	Kendall's tau-b	-.422	,103	-3,783	,000
	Kendall's tau-c	-.425	,112	-3,783	,000
	Spearman Correlation	-.483	,115	-3,936	,000(c)
Interval by Interval	Pearson's R	-.551	,113	-4,719	,000(c)
N of Valid Cases		53			

a. Not assuming the null hypothesis.

b. Using the asymptotic standard error assuming the null hypothesis.

c. Based on normal approximation.

**Table 18: Measures of correlation between degree of confidence in choice and perceived relevance of missing information (before PL reading).**

In the post PL phase same correlations between decision categories are confirmed: degree of confidence is positively correlated to the perceived level of information:  $\tau$  .419 (.000,  $n = 54$ ) and negatively correlated to the perceived relevance of missing information:  $\tau$  -.332 (.001,  $n = 51$ ).

An additional question introduced in the post PL phase as to elicit the subject's intention to further enquire about the drug (Q. 49: "Would you look for further information before keeping on with the therapy?"), has been found to be correlated to the perceived relevance of missing information:

Symmetric Measures					
		Value	Asy mp. Std. Error <sup>a</sup>	Approx. †	Approx. Sig.
Ordinal by	Kendall's tau-b	,355	,110	3,076	,002
Ordinal	Kendall's tau-c	,339	,110	3,076	,002
	Spearman Correlation	,395	,123	3,012	,004 <sup>c</sup>
Interval by Interv:	Pearson's R	,355	,129	2,658	,011 <sup>c</sup>
N of Valid Cases		51			

a. Not assuming the null hypothesis.

b. Using the asymptotic standard error assuming the null hypothesis.

c. Based on normal approximation.

**Table 19: Measures of correlation between desire to further enquire about the therapy and perceived relevance of missing information (after PL reading).**

The relationship between the intention to look for further information and the perceived relevance of missing information is significant especially because of the considerable coincidence of 0 assessment cases in both variables. The relationship is however strong for low assessments and loosens for high assessments: whereas a low intention to look for further information is related to a low relevance perception of missing information, the reverse does not hold, and participants might desire to further enquire about the therapy even if the missing information is not material for the decision.

This finding might hint at a gap between the desire for information and the potential impact of this information on the decision in the therapeutic setting.

## 6. Decision parameters and desire to further enquire the doctor

The parameter measuring the desire to further enquire the doctor after PL reading has significant correlations with almost all variables measuring decision dimensions: degree of confidence, perceived information level, uncertainty about a specific topic of concern, perceived information promise (persuasion, that it will remove uncertainty), and general intention to look for further information before keeping on with the therapy.

The negative relationship between degree of confidence in choice and desire to further enquire the doctor is mostly due to the distribution of the 100 assessments of enquire intention:

Symmetric Measures					
		Value	Asy mp. Std. Error <sup>a</sup>	Approx. †	Approx. Sig.
Ordinal by	Kendall's tau-b	-,380	,132	-2,871	,004
Ordinal	Kendall's tau-c	-,360	,125	-2,871	,004
	Spearman Correlation	-,419	,149	-3,097	,003 <sup>c</sup>
Interval by Interv:	Pearson's R	-,420	,145	-3,103	,003 <sup>c</sup>
N of Valid Cases		47			

a. Not assuming the null hypothesis.

b. Using the asymptotic standard error assuming the null hypothesis.

c. Based on normal approximation.

**Table 19: Measures of correlation between desire to further enquire the doctor and degree of confidence in choice (after PL reading).**

Subjects with absolute confidence in decision distribute unevenly between the two extreme values of absolute no or a totally strong intention to further enquire the doctor: most of the respondents with very high degree of confidence assign a 0 score to their desire to further enquire the doctor.

The intention to further enquire the doctor is vaguer for participants with a moderate to high degree of confidence in choice.

The intention to further enquire the doctor is positively related to the perceived level of information after having read the PL too. Because most of the participants have a very high perception of information level, the relationship is mostly due also here to the distribution difference of high perceived level of information cases in the groups 'absolute no intention to enquire the doctor again' (0) and 'extremely strong intention to enquire him again' (100): most of respondents with high perceived level of information assign a 0 score to the intention to further enquire the doctor. The table gives significance levels for this association:

Symmetric Measures					
		Value	Asy mp. Std. Error <sup>b</sup>	Approx. <sup>†</sup>	Approx. Sig.
Ordinal by Ordinal	Kendall's tau-b	-,371	,112	-3,280	,001
	Kendall's tau-c	-,364	,111	-3,280	,001
	Spearman Correlation	-,432	,129	-3,214	,002 <sup>c</sup>
Interval by Interv:	Pearson's R	-,432	,127	-3,213	,002 <sup>c</sup>
N of Valid Cases		47			

a. Not assuming the null hypothesis.  
b. Using the asymptotic standard error assuming the null hypothesis.  
c. Based on normal approximation.

**Table 20: Measures of correlation between desire to further enquire the doctor and perceived level of information (after PL reading).**

The relationship between general intention to further enquire and specific intention to enquire the doctor is more articulated.

Whereas uncertain and high intention to look for further information is significantly related to the intention to enquire the doctor again, extremely high intention to search for further information is equally distributed among absolute no intention and very strong intention to enquire the doctor:

Symmetric Measures					
		Value	Asy mp. Std. Error <sup>b</sup>	Approx. <sup>†</sup>	Approx. Sig.
Ordinal by Ordinal	Kendall's tau-b	,363	,127	2,819	,005
	Kendall's tau-c	,340	,121	2,819	,005
	Spearman Correlation	,399	,148	2,889	,006 <sup>c</sup>
Interval by Interv:	Pearson's R	,436	,131	3,216	,002 <sup>c</sup>
N of Valid Cases		46			

a. Not assuming the null hypothesis.  
b. Using the asymptotic standard error assuming the null hypothesis.  
c. Based on normal approximation.

**Table 21: Measures of correlation between desire to further enquire the doctor and intention to further enquire about the therapy in general (after PL reading).**

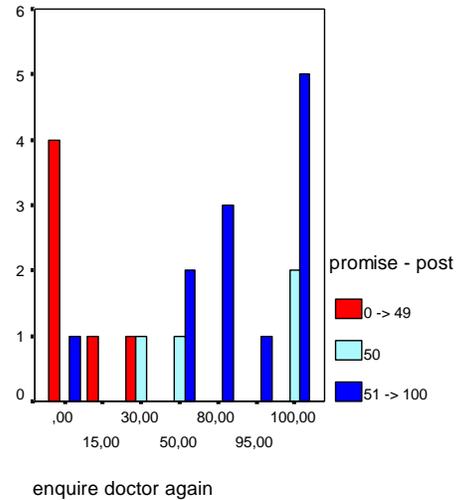
Similarly to the correlation regarding the desire to enquire the doctor, and the presence of a topic of uncertainty, this finding can be explained by the fact that extremely high intention to look for further information before keeping on with the therapy after PL reading might be associated with a certain trust loss in the physician at least for a portion of the sample.

The correlation between low scores is due to semantic reasons: the absolute lack of intention to look for further information presupposes the lack of intention to enquire the doctor. However, some respondents declare to have no intention to further enquire before keeping on with the therapy, and still manifest a high desire to enquire the doctor about it. This might be the result of a strict interpretation of the enquire question (enquire on my own).

The most interesting relationship regards the correlation between the persuasion that further information will remove the uncertainty (promise) and the intention to enquire the doctor again.

Symmetric Measures					
		Value	Asy. mp. Std. Error <sup>a</sup>	Approx. $\dagger$	Approx. Sig.
Ordinal by Ordinal	Kendall's tau-b	,546	,149	3,363	,001
	Kendall's tau-c	,564	,168	3,363	,001
	Spearman Correlation	,628	,161	3,612	,002 <sup>c</sup>
Interval by Interval	Pearson's R	,716	,131	4,587	,000 <sup>c</sup>
N of Valid Cases		22			

- a. Not assuming the null hypothesis.
- b. Using the asymptotic standard error assuming the null hypothesis.
- c. Based on normal approximation.



**Left: Table 22: symmetric measures of correlation between the intention to further enquire the doctor and information promise. Right: bar diagram, where bars height refers to the frequency of cases corresponding to different degrees of information promise.**

As the diagram illustrates, the intention to enquire the doctor is linked to the persuasion that the information will remove the uncertainty. Interestingly, the same relationship does not hold for the intention to introduce further information in the PL. Neither are other decision dimensions (degree of confidence, information relevance to decision, perceived information level, information promise) found to be associated to the parameter measuring the desire of further information in the PL.

The data presented in this section illustrate a relative consistency of interrelations among decision dimensions. This seems to be at odds with the substantial lack of regular relationships among these variables and risk/benefit assessment changes after reading the PL.

This gap can be the sign of different interrelated phenomena:

1. With certain respects, health information seeking is Bayesian: i.e. it is proportional to the information need in the context of a decision, moreover confidence in decision is proportional to the perceived level of information.
2. The fact that PL reading does only irregularly impact the benefit and risk assessments, notwithstanding its explicitly acknowledged importance can be due to a gap between its perceived value and its usability;

3. The high correlation between perceived uncertainty about a specific topic of concern, need for further information and intention to enquire the doctor again rather than desire to have more information in the PL precisely hints at this phenomenon, in that expert information is tailored to the individual both with regards to its form and its relevance.

Along these considerations, the importance of PL information as a source of information for consent should be probably toned down and reconsidered, all the more because only an exiguous part of the participants did show awareness of its legal nature as liability disclaimer (21,8%).

## 7. Study limitations

The results of this exploratory study are rather fragmentary and do not allow for the construction of a theoretical model. The following points highlight the limits affecting the analysis:

1. The sample characteristics do not allow measuring the effect of PL information on respondents assigning low reliability to the doctor as an information source, because the great majority of participants assign an extremely high reliability score to the doctor. In certain respects this might also be the reason for a lack of systematic differences within the parameter measuring the degree of shared decision making vs. delegation to the doctor in relation to the risk and benefit assessment changes. In fact, greater decision autonomy (for instance in shared decision making) should predict more variance after consulting an additional source of information (in this case the PL), whereas choice delegation should predict a tendency to conservatism. Neither of the two associations has been observed in this sample.
2. The distinction of benefit and risk into two distinct parameters may find the lay assessor unprepared: the separation of these two components is rather artificial and contrary to observed cognitive processes of patients' health information processing.<sup>602</sup> However with respect to this point two considerations are needed:
  - i. The extent to which this separation is artificial for the lay appraiser determines the measure of perplexity in making a personal risk/benefit assessment on the basis of disconnected benefit and risk data.
  - ii. Our study allows this type of uncertainty to be expressed in the "I can't judge option". Even if this option might be crossed also because of genuine uncertainty, still it remains the fact that whenever participants have opted for making a benefit and a risk assessment, they can't be said to have been forced to do so.
3. Another hot topic in the field of risk learning is the lay interpretation of probabilistic risk assessment: scholars' debate about the lay capacity to rationally update probabilistic information and to deal with probabilities without falling into computation fallacies or biases.<sup>603</sup> Indeed this study was also aimed at observing the

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<sup>602</sup> Vander Stichele, 2002: 206; Alkahami, Slovic, 1994: 1090.

<sup>603</sup> Supporter of lay fallacy in dealing with probabilistic assessments: Kahneman, Slovic, Tversky 1982; Bar-Hillel 1980; Kahneman, Tversky 1982, 1973, 1972; Tversky, Kahneman 1983, 1982, 1974, 1971.

effect of PL information in terms risk and benefit estimation updating: no evidence of a systematic computation has emerged from the data. However this cannot corroborate the hypothesis that lay assessors do not integrate different data rationally (either in a Bayesian fashion or adopting heuristics), because the experiment design could not control for an important unobservable parameter in this respect: the level of desired information accuracy. Indeed it has been acknowledged<sup>604</sup> that information processing – which entails the integration of old and new knowledge – is performed at different levels of precision depending on the task at hand and the expected cost of information elaboration and knowledge updating.

Therefore the lack of systematic correlations between past knowledge, PL information and risk and benefit updating can be due to different levels of precision in information processing, which on its turn depend on the expected value of information to the decision and the expected cost in relation to the perceived personal capacity to deal with the information.<sup>605</sup>

4. Another strong limitation of this study regards the lack of a control group for the identification of reappraisal and cognitive dissonance strategies in processing risk information. This should have been composed by healthy participants not concretely concerned by the drug risk exposed to the same treatment (PL reading). The difference between the average changes in the two groups could then be ascribed to self-reassurance strategies, such as reappraisal and cognitive dissonance.<sup>606</sup> In general the intent to investigate risk and benefit updating with participants really concerned by a choice has strongly limited the design sophistication with the consequent lack of control over many latent variables.

5. Obviously the main limitation of this study regards its extremely reduced sample size and therefore low level of representativeness.

The size dimension has also made impossible any sophisticated analysis of the data, such as factor analysis, regression analysis, or even the simple control for common causes of interrelated parameters.

Notwithstanding these shortcomings, the study presents interesting phenomena worth of further investigation.

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Advocates of the lay capacity to deal with probabilistic information ascribe these fallacies to economic shortcuts and heuristics: Gigerenzer, 1998, 1996, 1994, Gigerenzer, Hofrage, 1995; Gigerenzer et al. 1999; Cosmides and Tooby, 1996; Kleiter, 1994, Kohler, 1996; Girotto, Gonzales, 2001; Reyna et al. 2003. See also Magat, Viscusi, Huber, 1987, and Viscusi et al., 1987 who provide findings of lay rational probabilistic updating.

<sup>604</sup> See Kahlor et al. 2003; Reyna et al. 2003; Dougherty et al. 2003; Martignon and Krauss, 2003, Schneider Schanteau, 2003; Griffin et al. 2002; Gigerenzer, 2001; Slovic, McMackin, 2000; Gigerenzer et al. 1999; Trumbo, 1999.

<sup>605</sup> This explanation integrates the classic Bayesian account of expected value of information with cognitive accounts of information processing: more on this in the last chapter.

<sup>606</sup> These phenomena have been recurrently observed in the literature devoted to health risk information processing: Preuss, 1986; Bealneaves, Long, 1999; Steckelberg, 2004b, 2005. More details in the last chapter.

## 8. Summary and conclusion

Assessment changes seem to be differently influenced by the decision parameters. The following table summarizes the results:

	Assessment changes					
	General benefit	General risk (quantity)	General risk (severity)	Risk/benefit assessment	Personal risk	Personal benefit
a. Perceived level of info			✓			
b. Health condition			✓	✓		
c. Past experience		✓ (with SE)		✓ (with benefits)		
d. PL info	✓ (tot)		✓ (indefinite SE)		✓ (numeric frequency)	
e. Level of concern				✓	✓	
f. Risk acceptance					✓	
g. Degree of confidence					✓	

- a) Increased risk severity is associated with the absolute uncertainty to have further information in the PL.
- b) Participants affected by a light disease are more likely to increase their risk assessment both in terms of severity and in the overall risk/benefit assessment.
- c) A positive past experience with drug benefits is associated with benefit increase in the risk/benefit assessment. Furthermore, all respondents assessing a higher than average experience with side effects (score: 51 to 100) also increase their risk assessment in terms of quantity after reading the PL.
- d) PL content acts as an inhibitor of risk quantity assessment increase whenever the light side effects in the list are lower than average. Lower than average number of all side effects also fosters benefit assessment increase.
- e) The level of concern is the only parameter significantly associated with both personal risk assessments. Both high and low levels of concern are related to *personal* risk assessment increase whereas a medium level of concern bears no association with any change pattern. Instead, low and high level of concern are associated to increase and decrease of risk in the risk/benefit assessment respectively.
- f) Respondents declaring low risk acceptance more probably increase their personal risk assessment after reading the PL. This is also valid for uncertain respondents. Instead participants declaring high risk acceptance spread all over the change distribution with high modality on the 0 value (no change).
- g) Respondents with high degree of confidence in choice decrease their personal risk prognosis or leave it unchanged, whereas participants with low to high confidence tend to increase it.

The observed associations (a-e, and 2) have been traced back to heterogeneous sources of bias in risk learning:

- ii. *Cognitive dissonance*. This phenomenon has been long recognized as an important aspect of information selection and processing:<sup>607</sup> people tend to select and store information which confirm their opinion or their wishful thinking: “rewarding information”. Cognitive dissonance might explain associations a, c and g.
- iii. *Lack of distinction of risk and benefit as separate entities for the lay assessor*. The health technology tends to be considered as a whole without clear-cut separation of benefits and risks.
- iv. The conjunction of factors I and II may explain the increase of benefit assessment for participants with a PL containing lower than average number of side effects (d), and the association between the presence of a topic of uncertainty and a lower benefit assessment (general and personal) (2).
- v. *Reappraisal strategies in the face of uncontrollable risk*. These strategies lead to act on the risk perception whenever it is not possible to minimize or avoid the risk itself: this might explain the decrease in risk perception after reading the PL. Risk reappraisal seems to hook in this case on a pragmatic cue: the lower than average number of side effects in the PL (d).
- vi. *Prospect theory*. Both parameters health condition (b) and level of concern (e) seem to reflect the considerations developed within prospect theory. This theory accounts for risk proclivity vs. aversion by considering the status quo of the decision maker with respect to the prospect offered by the options available (loss or gain). In the health condition parameter, *participants with a light disease will tend to risk aversion and therefore perceive the drug risk as higher than the inconveniences brought about by their illness, instead people with severe diseases will tend to be risk prone and therefore have higher tolerance for the drug risk*. This is also partly confirmed by the relationship between low risk acceptance and increase in risk perception.
- vii. *Level of information processing accuracy*. This phenomenon might function as an alternative explanation to the reason why both low concerned participants and high concerned ones increase their *personal* risk perception after reading the PL (e): both low and high level of stress predict less than accurate information processing and can lead to over-alarm or risk underestimation (reappraisal).<sup>608</sup>

The main result deriving from this study is however the gap between increased perceived level of information and

1. insignificant PL impact on benefit and risk assessments;
2. absolute no impact on the decision.

The presence of a specific topic of concern seems to have some effect on the degree of confidence in choice and on the personal benefit assessment before reading the PL. In the post-PL phase the persistence or emergence of a specific topic of concern is associated with lower degree of confidence in choice, less favourable risk/benefit assessment, lower benefit assessment (both general and personal), and higher desire to further enquire about the drug.

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<sup>607</sup> Frey, 1982.

<sup>608</sup> See Bealneaves, Long, 1999.

However, the presence of a specific topic of concern seems to have no influence on the final decision which remains as definite as before (100 score for all participants). Considering the generally positive evaluation of PL information and the increased perceived level of information after PL reading, these data support the hypothesis that the therapeutic decision concerning prescription drugs is quite insensitive to PL information. The concept of decision sensitivity can indeed provide the framework within which cognitive dissonance, reappraisal strategies, level of information processing accuracy – can be subsumed and investigated in an integrated picture. This enterprise will be undertaken in the last chapter of this work.



## 8 **PL information processing: the relevance paradox**

*What patterns of experience would justify calling a connection “causal”? Moreover:  
What patterns of experience convince people that a connection is “causal”?*  
Judea Pearl, Causality, 2000.

### **1. PL information processing: Think-aloud experiment**

The quantitative analysis has evidenced a discrepancy between the importance attributed to package leaflet and their exiguous impact in the development of an autonomous risk/benefit assessment: the degree of confidence in the decision seems to be hardly shaken by PL reading.

More importantly increased awareness perception never leads to a decision change. The hypothesis has been advanced that the decision settings of the survey participants were not sensitive to PL information.

However the presence of a specific topic of concern rather than the undifferentiated amount of PL information has been found to be associated to important parameters such as the degree of confidence in choice and the risk/benefit assessment.

This chapter is devoted to investigate PL information selection and the dynamics related to the presence of uncertainty through a qualitative study.

In the survey context 15 participants accepted to fill in the questionnaire in the presence of the analyst [the author of this study] in a think-aloud fashion. The analyst task was limited to record commentaries and eventually elicit responses when subjects found it difficult to give an answer whatsoever. Additionally, also the written comments to open questions given by the other participants in the questionnaire have been integrated into the corpus.

### **2. Health risk information avoidance**

The first phenomenon observed from the first interviews has been the reluctance with which PL texts were dealt with, and the exceptional status of reading the entire text.<sup>609</sup> Reluctance to systematically process PL information is artificially acted against in the special interview context.

Interview 14 provides an example of this sort of phenomenon:

(813) I: “I [...] not always. Well, I don’t read it so intensely as I read it now”.

(875) I: (To the question whether the questionnaire is interesting): “At any rate it is interesting, because I reflected over things, because before I never reflected it over that way”.

(897) I: (To the question whether the questionnaire is useful): “Also for myself – yeah. Yes, because I am involved for the first time so intensely with it, and I see that in fact something is wanting”.

Generally there are explicit requests to obviate reading the PL, and indeed many participants show a real aversion to PL information:

# 8: Q.16 (Information source reliability – PL: Score: 50): “They [...] a total confusion, when you read that –“

“*But is it reliable or not?*”

“What shall I say – you have to trust them, you can – otherwise you can prove nothing, can you? I find there’s too much on such, too much in these –“

# 8, 1: “Can’t we simply find out what concerns my illness?”

# 8, Q. 38: “*Now some questions about your reading experience. In reading the PL it was important* “Countermeasures to side-effects: then I don’t need to read the all thing through”.

# 13“Completely boring, but ok [I keep on reading it]”.

# 14, 437 ff. “*Ok. Now let’s start read the PL. You read and I write down your comments, Anyway they are also [recorded]*”

“Read side effects or?”

“*No, from the beginning, everything*”

“Everything from the beginning? Oh bother!”

Feelings of uneasiness in dealing with PL information are also explicitly expressed:

Interview # 8:

Underlined text passages	Comments
19) Frequency table	„These numbers don’t concern me at all“ „ <i>In what sense?</i> “ „Because actually I have ...– „ <i>very often</i> “ – I don’t make all these trials there – one should evaluate it but one didn’t participate in it“.
20) „Central nerve system. Very seldom, an aseptic meningitis (inflammation of the meninges not caused by pathoenes) and head aches were reported	„ <b>They make you anxious, when you have a little head-ache, you should immediately think, that it is ..., no</b> ”
21) „Hallucinations“	„No, you can forget it“.
22) „Arthralgy (rheumatism)“	„What shall I say? This has nothing to do with my – that my knee is ill here, that I feel pain here. That is – well you can forget it. This goes back to old times, what you have here – this has nothing to do with it [the drug]”.
23) “Sense organs: Eye. Transitory	“You can forget it too. My eye – this is – they

<sup>609</sup> This datum is not at odds with the quantitative datum that almost all participants declare to regularly read the PL (71,3%, see chapter 8, § 3.3), because this does not imply that they read it all.

shortsightedness and inflammation of the choroids were seldom observed”	have nothing to do with it. Ok, I have a glaucoma, that is treated with eye-drops. You cannot see the difference. They are always the same now”. “What is the difference that you cannot see?” “That something worsened because of these tablets. That’s not possible at all”.
24) „Lever and pancreas“	„No, you can forget it“
25) “Hypokaliemy (reduction of kalium in the blood) or hyperkaliemy (increase of kalium in the blood): in connection with Hyponatriemy”	“No, you can go on, you can forget it too”. “Why?” “Because it does not concern me”. “And why?” “Why? That is-” “Metabolism. Do you know what’s about?” “Metabolism and blood- mineral – no – no, forget it, otherwise you go crazy here. You fall ill, when you read all that through. What have you had”.
26) „Very seldom. Hypersensitivity reactions at the lungs“.	„You can forget it at the lungs I have nothing, nothing”.
27) „Blood (the entire paragraph)“	„None. These tablets, I got them also in the hospital now, and nothing of what was read has come off. And now I take them at home and nothing happens“.
28) „Hypersensitivity reactions. Aalergic reactions. Skin and mucus“.  „Rash, redness, spots, lumps, or-“	„Nothing. Look, when now I take half a dosis – but for the first time at home – and what big things can you expect to happen-,,  „No, I have none of these, no the skin is normal“.
29) „Countermeasures to side effects“	„This is maybe the most important chapter. This is what one should pay attention to”.

Two cases mention anxiety as a reaction to learning “bad news”:

- # 16, 3: “Side effects”: “When you read this, you wouldn’t like to take the treatment”.
- # 34, 2: “Precautions. Drug interference” (the entire paragraph is marked): “New. Frightening”.
- # 34, 4: “Side effects” (the entire paragraph is marked): “Frightening”.

These excerpts confirm the phenomenon of health information avoidance as already acknowledged in the literature<sup>610</sup> and explained through the theory of cognitive dissonance,<sup>611</sup> and reappraisal strategies<sup>612</sup>.

### 3. PL information selection

The experiment has evidenced an extensive selection of PL information by the lay reader.

Many participants show to be self-confident in filtering out what they deem to be personally irrelevant information, as the following example illustrates:

<sup>610</sup> Åstrom et al., 2000; Duggan, Bates, 2000; Laaksonen et al., 2002. See also next chapter.

<sup>611</sup> Steckelberg, 2005b, 2004.

<sup>612</sup> Afifi, Weiner, 2004; Bealneaves, Long, 1999; Preuss, 1986.

Interview #6:

Underlined text passages	Comments
1) „Precautions: Thyronajod 75 Henning cannot be taken if you are hypersensitive towards the chemical entities or other components contained in Thyronajod 75 Henning“.	Am not
2) When you are affected by thyroid hyperfunction	Neither
3) When the thyroid shows areas that produce thyroid hormone irregularly ... In this case no treatment should take place, even by not yet unambiguous thyroid hyperfunction.	I have no hyper-function too.
4) When you are affected by one of the following diseases or one of the mentioned conditions: A recent heart infarct; An acute heart muscles inflammation An acute heart inflammation.	don't. don't either. <i>Don't either ... What is an acute heart inflammation? What ist that?</i>
5) Before starting the therapy you must exclude or treat following diseases: coronary vessels disease pain in the heart regions blood vessels calcification High blood pressure  Pituitary gland feebleness.	Don't have Don't have either neither <i>In the meanwhile I have it, but before I didn't. This is obviously something, that I should clear up: one should enquire again.</i> Don't have

# 6, Q. 33: “Now some questions about your reading experience: While reading the Patient Package leaflet it was important ... To compare the information with my experience with treatments”.  
*“How did you select the information?”*  
 “What was important for me and what not”.  
*“And according to what did you decide, that something was important and other things not?”*  
 “Because most of the things did not concern me”.

In these excerpts most precautions and warnings are rapidly got rid of with no residual uncertainty (topics of uncertainty are printed in italics and will be treated later on in this chapter). A strong similarity to this pattern can be seen in interviews 9, 11, 13, but this phenomenon leaks out in any of the interview. This obviously strongly depends on the familiarity with the drug. However, also participants processing information about a new drug (as an example take #14) are far from taking into serious account all the information available.

We may roughly quantify this phenomenon with the help of our data by calculating the ratio between the number of side effects explicitly taken into account while reading the PL and the total number of side effects actually mentioned in the list. In our corpus of interviews the mean percentage of side effects actually taken into account by the reader (included those from which he excludes to be possibly affected) is 28%. In order to appreciate how low this figure is, one should consider again the artificial setting of the interview, and how this elicited a much deeper attention than normal, in prompting the participant to give account of the text.

Principally there is no reason for discounting the drug from causing each of the side effects mentioned in the list. The question is therefore: How do drug consumers distinguish personally relevant information form irrelevant data?

The “think-aloud” procedure has brought to light some implicit shortcuts, which the readers use when faced with the necessity of assessing personal relevance of side effects.

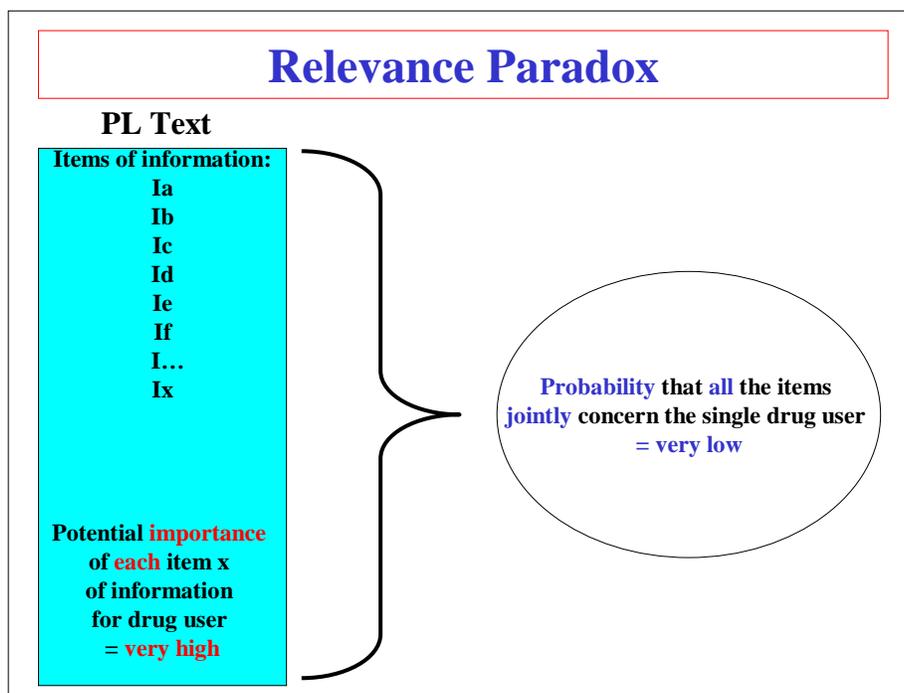
### 3.1 The relevance paradox

In the quantitative analysis, PL information is evaluated as not excessive by 60% of the respondents. However, 29,1% of them declare absolute no desire to introduce additional information in the PL after reading it, and almost the half of them would rather have no further information in the PL.

This phenomenon might be explained as follows. On the one hand, the PL text has on principle a high personal relevance associated to high stake goods such as health and well being. Therefore any piece of information contained in it has virtually extreme importance and cannot be done away unless one feels justified in neglecting it for some reason.

On the other hand, the probability that all the items of information will jointly concern the reader is extremely low. Indeed only a minor proportion of the information items do refer to the special health condition in which the reader finds himself.

This situation produces a phenomenon which I called ‘relevance paradox’: considered as a whole, the PL text provides much more quantity of information than needed, because the probability that all of it will concern the single reader is very low, but the importance of each item of information is generally very high:



**Figure 15: Relevance paradox for the PL text: each item of information might result to be very important for the user, but the conjoint probability that all the PL information concerns him is very low.**

The awareness that the message is directed at any potential user of drug x, leads the single user to consider the text as constitutively over-informative: there are so many peaces of information as many traits related to all the individuals who might use this drug. Since only few of these traits concern any single individual, most of the information is for each addressee superfluous and not worth processing. The question however arises as to the criteria of this selection, given that the average drug consumer does not possess sufficient competence to discriminate relevant from irrelevant information.

### 3.2 The PL as a co-text to doctor's information

One factor that helps explain the confidence with which readers filter out irrelevant information traces back to coherence aspects of knowledge updating.<sup>613</sup> The selection of PL information is a function of its familiarity with old knowledge, especially if previously acquired from the doctor in the prescription phase. In this sense the PL can be also said to function as a co-text to what already learned during the consultation. In the interviews this phenomenon especially comes to light either through explicit text account on the light of doctor's quotations or through discrepancies noted between instructions given by the doctor and the terminology used in the PL:

# 1, 7: "*Interference with other drugs*": "I may take head-ache tablets, told me the doctor, when I don't have head-ache every day".

# 4, 3: "*Indications. Mizolastin is long effect H<sub>1</sub>-antihistaminic, that is indicated for the symptomatic treatment of season allergic rhino-conjunctivitis (hay fever), of perennial allergic rhino-conjunctivitis and of urticaria*":

"I have hay fever... Skin problems. The doctor said, the skin becomes sensitive through all the allergies".

# 5, Q. 39: "*I find this information ... already known (Score: 50)*": "Yes, indeed my doctor told me what can happen".

Note that the score associated to the last comment is not 100 but 50: from this the reader manifests the belief that half of the information is old for her, however also letting understand that this information is assumed to exhaust the entire range of possible events that can concern her. As a consequence the half of unknown information can be dismissed as not concerning her.

The following two examples are especially interesting in this sense. Not only does the knowledge acquired in the consultation acts as a filter for PL information, but also the way around, some information contained in the PL may prompt actualization and further elaboration of doctor's instructions. In the first example an adverse reaction, which in itself could bear no personal relevance to the reader, gains salience by finding connection to the instructions given by the doctor:

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<sup>613</sup> For a formal treatment of these phenomena see: Gärdenfors, 1988; Bovens, Hartmann, 2003.

# 13, 15: “*In single cases blood circulation disturbs of the littlest vessels in the skin (skin infarct) and the dying out of little skin areas (skin necrosis) were observed*”:

“Yes, here I ask myself, if this is what the doctor meant: ‘pay attention to bigger brown spots on the skin – then inform me immediately’”,

#13, 16: “*In some cases, this led to death or permanent disability*”:

“Ah, cool, that’s cool: in some cases – mhm what are skin necrosis spots like? – they might be brown”

# 13, 17: “*It seems that necroses are accompanied by local thromboses, the occurrence of which takes place some days after beginning the anticoagulant therapy*”

“Yes ehe – then now I could – indeed I don’t need any more to pay attention to it, well it must be something else”.

The information coming from the consultation – ‘Pay attention to bigger brown spots on the skin’ - is retrieved and made available for processing PL information which is at first incomprehensible (“skin necroses” #13,15). If a matching between the doctor’s instruction and the PL information can be ascertained, then context enrichment takes place: both the doctor’s instruction is integrated in a wider model, and the PL warning can be better understood (#13,16). Until this point, the doctors ‘brown skin spots’ are still identified with the ‘skin necrosis’ in the PL text. But thereafter, further information about inception time turns out to contradict observation (the patient has been taking the tablets already for some months now), then following interpretation steps follow (#13, 17):

1. necroses are accompanied by thromboses which appear at the therapy beginning;
2. the fact that they did not materialize until now makes the probability of their occurrence negligible;
3. therefore I don’t need to pay attention to the skin spots any more.

The reader realizes that this very identification is not sufficiently supported by the elements at hand and therefore leaves the topic there. The context enrichment is abortive.

Context enrichment phenomena prompted by “intertextual” inferences come in interview 14 even more explicitly to the surface: the filtered processing strategy is illustrated by several linguistic traces, which manifest the interaction between background information and PL processing.

The point at which the excerpt starts is where the first part of the questionnaire has already been answered, and the PL reading follows:

460 I: {h} mhm. Indications (4) here we have already *grampositive gramnegative*  
461 *pathogens* [mhm] never heard of. I heard Staphilococcus (6) mhm (.)  
462 but here there are always so many special terms (4) but [...] only the all list (.)  
463 of the diseases for which this treatment is indicated – it tells me nothing.  
464 Everything in Latin. (3) And sometimes absolutely unpronounceable. [hh] well, it  
465 mostly doesn’t mean a thing to me.  
466 Q: But is there anything that -  
467 I: - that I can **recognize again**? Absolutely not.  
468 Q: Nothing [no] really?  
469 I: No. Well, I **recognize** *Pathogen* and think, ok Pathogen is what the doctor said  
470 – *Germs, Bacteria* [ok] I think, ok – this was also – by the doctor – but  
471 what exactly, well I, *E. coli* I don’t suppose [mhm] and everything else, that  
472 is there - I can tell – difficult – I can tell absolutely nothing [mhm] – I can  
473 definitely tell nothing [mhm ok] I have only pathogen **back** and - [mhm mhm] I  
474 know that I have it. Also here: *It is indicated for the treatment of infections, that*  
475 *are caused by germs sensitive to Sulta (.).micillin-* I don’t know, if the germ was  
476 sensitive against it for it, or whatever [mhm] anyway (.) I know that I had a germ

477 and that it has caused the infection, but whether it was sensitive to that there (.)  
 478 [mhm] no doctor told me. I don't know it ehm - I reads on (6) – *it is for the skin*  
 479 *and private parts* (..) so it is fort the skin actually, this is comprehensible, here I  
 480 find myself again - [mhm] (13)  
 481 contraindications (11) e – this happened to me too. Before the – *before the therapy,*  
 482 *eventual sensitivity reactions to Cephalosporin and other allergens should be*  
 483 *carefully investigated.*  
 484 Q: Did he ask you if -?  
 485 I: Well in the end not, no: - Is it what he asked me, when he asked me, whether  
 486 I am allergic to Penicillin? [ja] Is it? [ja] Ok, then he asked me. But then  
 487 I don't know again (..) what are Cephalosporin and other allergens. Had it  
 488 directly said ‚Penicillin’ – so that it refers directly (.)  
 489 to Penicillin-  
 490 Q: Yes, it's a type of it-  
 491 I: Yes, but this is what I mean, this technical language in there (..) [exactly] [...] does  
 492 not mean much - well: [mhm mhm]

Line 467: “- that I can recognize again (in the original: Das ich wieder erkenne?”) tells us much of how the reader processes PL information: As the questioner of the interview, I was trying to elicit some comments to the PL (466), and, if not interrupted by the interviewee, I would have ended the question by asking if there was something that *caught her attention*. Instead the interviewee has given a completion in a completely different direction, which has surprised me.<sup>614</sup>

By interpreting the task of commenting the PL as a request to identify already known information, the interviewee explicitly mentioned the tacit criterion, which she resorted to in interpreting this sort of information. *This criterion is constituted by drawing on old familiar knowledge and matching as much PL information as possible with it.*

How inferences and recognition patterns work in this sense needs further investigation. For instance, what makes the reader reflect about the penicillin question (lines 482-91)? It seems that the only way she could have come to connect cephalosporin with penicillin is via the word “allergens”. It might be that searching in her “data base” for the piece of knowledge which most suited the information at hand, she remembered about the doctor asking her if she was allergic to penicillin, and then, given that no other ‘allergy issue’ had emerged during the consultation, she inferred that penicillin and cephalosporin could be the same thing. Still, context enrichment could take place only after verifying the soundness of the inference by asking to the questioner.

Awareness of the role played by the knowledge provided by the physician can help us identify the rationales underlying information selection.

In the PL context, one might hypothesize that, the higher the trust in the physician (and generally the lower any motivation factor to process information autonomously) the stricter will the reader adhere to the ‘agenda’ given by him. Any information with no relationship to any item of knowledge in one’s own database is perceived as

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<sup>614</sup> Elizabeth Gülich (personal conversation) let me notice that completion of the communication partner’s line is a much studied conversation phenomenon in linguistics (so called “co-enunciation”). A more detailed discussion of this interesting phenomenon is unfortunately out of the scope of this work.

irrelevant and dismissed as such. *Paradoxically one might say here, that information that sounds “new” at this stage of post-consultation, will be considered irrelevant.*<sup>615</sup>

### 3.3 Counterfactual neglect

The filtering process described so far is also acting at a pragmatic level: when information is encountered which not only ‘sounds new’ because it has not been mentioned by the physician, but which is also incomprehensible, either literally or in its health implications, then pragmatic maxims, such as the cooperative principle, build the basis for information selection. In fact incomprehensibility of words or text passages can be taken as an instruction to skip the text. In combination with the “co-textuality phenomenon” evidenced in the preceding paragraph, the reader might consider that information which he does not understand does not concern him, because otherwise he would have been informed about it by the doctor.

Counterfactual neglect can be considered as a pragmatic inference about health communication in the PL context: “if I cannot understand this piece of information, this means that it does not address me; therefore I can skip it”. The argumentation goes as follows:

*Counterfactual Conditional:*

if I were concerned by this piece of information

I would be informed about it – either through the doctor or through facts - (counterfactual);

*Real Facts:*

but I don’t even understand it,

which is a clear sign that I am not informed about that;

*Inference:*

therefore I am not concerned about it.

Counterfactual neglect cannot be presented with examples for obvious reasons, but the proof that skim reading and counterfactual neglect are deeply interrelated can be illustrated by the following comments:

# 8, 15: “*The contemporaneous use of anesthetization drugs ...*”: “This does not concern me either. If it concerns anesthetization, I have no influence there. It is the doctor that makes it ...”

# 10, 2: “*Contraindications*”: “Well, also this here is important: ‘Contraindications. When not ...’ but I don’t find this as important as the first one [indications], because for this, it is the doctor which is responsible”.

# 12, 11: “*Effects on blood and blood components*”: “How can you see it? Superfluous information: the doctor should consider it”.

#13, 6: “First something about contraindications: I would never read them. It does concern the doctor, before he pokes this in my paw, he must already have clarified -”  
“*Pardon?*”

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<sup>615</sup> The paradox however is only apparent, in that relevance is a relational dimension which is not only determined by novelty but also depends on the connection with old knowledge. See Sperber, Wilson, 1986: 143.

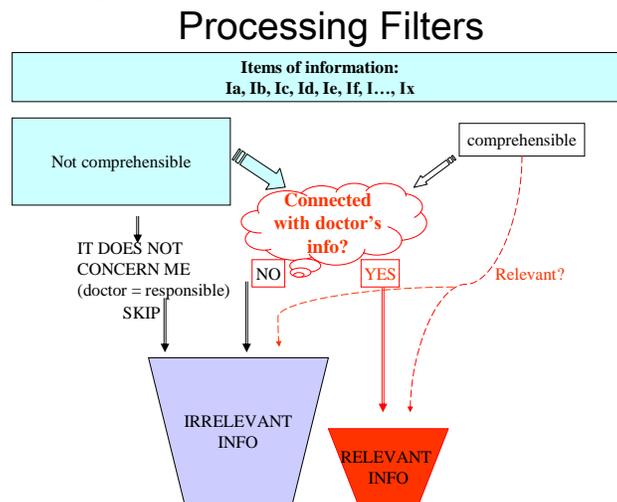
“ [hh] Well, I think, this is simply information, that can be done without by such a message, if you consider it as information for the patient, because this should have been clarified by the doctor – this is information that belongs to the doctor. You notice it also by the halting reading: which disease ...”  
 “And you cannot know if you have a risk for some diseases or -”  
 “No, no. Well, ok, maybe still by high blood pressure - or I can ascertain if I am pregnant, but the rest – this is somehow – this is completely in the wrong place [...] most of the information cannot be ascertained by the patient”.

# 13, 8: “*Angiography*. Completely a nonsense. There’s information inside it that absolutely – like angiography for instance. This concerns doctors and above these [...] On the other hand here – there are people [...] that must know this: this should be emphasized much more, this is [...] but it must be marked. – Children too – The leaflet is not adequate to the target group –”

# 50, 1: “*Thyronajod 50 cannot be used if you are hypersensitive (allergic) to the chemical entities or the other components contained in Thyronajod 50*”: “Incomprehensible. Only the doctor who treats can judge it”.

In these cases the conviction is explicitly expressed, that *what cannot be understood lies in the doctor’s responsibility*.

Counterfactual neglect and co-textuality with the doctor’s information jointly constitute the processing filters of PL information:



**Figure 16: Economizing filters in PL information processing. Not comprehensible information (the most part) goes unprocessed in the “irrelevant info” bin, unless a connection with doctor's information is established.**

When data are incomprehensible, the reader tends to treat them as not relevant (the doctor is responsible) unless a connection can somehow be established to what the doctor has said: in this case context enrichment takes place, and the information item falls in the ‘relevant info’ bin.

Where the peace of information is comprehensible and connected with the knowledge acquired through the doctor’s consultation, then it is considered undoubtedly relevant. It seems that incomprehensibility is taken as a pragmatic instruction indicating that the reader shouldn’t consider himself as the actual addressee.

Indeed, along these considerations, we can say that, the institutional context in which PL communication is embedded provides the pragmatic clues, through which PL information processing is at all possible. *Without the cues provided by the doctor’s information, the reader would find himself in front of an amount of unmanageable*

*information, which only becomes intelligible through the knowledge previously acquired in the consultation.*

On the other side, the expected outcome of any informative transaction is that information is shared. Therefore, questions of mutuality left for the moment apart, the patient can suppose to be partly responsible about the issues, that the doctor decided to communicate to him, especially for instructions related to aspects that only the patient has under control. As a consequence, on reading the PL, he will pay more attention to these aspects than to others.

Uncertainty may arise when the piece of information is comprehensible but not connected to the doctor's instructions. The bifurcation of the dashed red arrow stands for the uncertainty as to the personal relevance of this sort of data. For these, an autonomous interpretation space opens up, where personal relevance must be assessed recurring to other information sources: personal past experience or knowledge acquired from other sources than the doctor.

This case is illustrated by the following excerpt:

# 6, 5: "*Precautions. High blood pressure.* In the meanwhile I have it. But before I didn't have it. This is something that I must clear of course, one should enquire again".

# 6, Q. 43: "*I would like to talk again with the doctor about the treatment*". (Score: 100). Because, what makes me suspicious: I take this drug since – 96 Op, 97 – let's say 97. And since two years ago – was it two years ago? Yes, well no, three years, they diagnosed that I have high blood pressure. Well it NEEDN'T be in connection with the drug – it CAN though... this was under side-effects, wasn't it?"

"*No, under precautions*".

"BEFORE the intake. At the time I had no high blood pressure. That's it: '*Before starting the therapy you must...*' at the time I had no high drug pressure; i.e. before. I have been having it for three years now. But I will ask him nonetheless".

# 6, Q. 45-46: "*Is there anything left that makes you uncertain? What is it?*"

"Yes, well. On the other hand, this high blood pressure, they diagnosed it three years ago, since then I have been under treatment, and I also have always been anyway. The test results have always been in order. So from that, I am almost sure, that it does not have a connection".

The respondent seems concerned about a piece of information found in the precaution paragraph. This passage cautions subjects affected by high-blood pressure from taking the drug. As her blood pressure has indeed registered an increase in recent years, she entertains the hypothesis that the drug might have contributed to the development of this disturb. Her perceived incapacity to solve her doubts prompts her to express the desire to further enquire the doctor on the matter.

However, there are cases of uncertainty which are left unsolved with no trouble, presumably because they are not deemed worth of further investigation:

# 4, 9: "*Tiredness.* I am not 'power-charged' too, but you can't say if it depends on the drug".

# 9, 18: "*And do you notice memory disturbs or don't you, because it's also important for our job, an academic job-*"

"I have always had concentration or memory disturbs, but you never know what it is, if it depends on depression, with the anxiety, which compromises also the concentration capacity".

# 9, 20: "*Occasionally: tiredness.* I can't distinguish, if it comes from the drug or if it is a disease symptom".

# 15, 6: "*Nightmares.* This can depend on these tablets".

In these examples, it is evident that the uncertainty generated by PL information does not necessarily lead to further information need. *Uncertainty might be left unsolved, when stakes are not high enough to require active information seeking.* This is precisely the type of phenomena investigated within the framework of the Bayesian theory of expected information, which will be presented in the next chapter.

#### 4. Prognostic uncertainty

Generally, participants declare to read the PL, precisely in order to have an idea about what it may occur:

# 2, 1: "I always read it through and see what might come".

# 4, 1: "At the beginning [of the therapy] I read the PL, to know what may come, but as nothing happened."

# 4, 8: "I read at that time also to know what may come: incorrect use ... This is the most important for me. As the doctor's dose did not correspond to that of the PL, I read what could happen in case of overdose".

# 10, 9: "*Side effects ...*": "This is important"

"Do you believe that you might be affected by any of these side effects or you can exclude it without any worries?"

No, you cannot exclude it, well here the irritation and dryness of the nose mucus, you have to take it into account, well normally I have nose bleeding, I had never before that way – and here: *nose stimulation*, this is always the case. As soon as I take it, I must always sneeze, but this is normal".

# 15, 5: "*Nebenwirkungen ...* It can happen even if it has not happened before".

However a great variance characterizes the sample as to the epistemic status assigned to probabilistic information. In the test phase I happened to interview an old lady with a skin fungus: while reading the side effects list, I could see her nodding her head and saying: "This won't possibly affect me", "Neither this" and so on, but then stopped at the percentage frequencies and wondered: "What does it mean to me, that it seldom happens, or 1 out of 10.000 times. Either does it happen to me or not. There's no graduation". This is what might be called a radical frequentist attitude.<sup>616</sup>

A similar example is in questionnaire # 55:

# 55, 4: (about the frequencies accompanying the side-effects list).

"What side effects are possible? Very incomprehensible for me. Seldom or very seldom: either, or. So one can also do without writing side-effects".

The most typical reaction to risk information is a sort of helplessness feeling:

# 14, 175 ff: (Reliability of info sources) "You mean, whether it's correct what you find there or it's not. This is also a thing; generally speaking, I don't know it. Precisely as far as side effects are concerned, well not necessarily with reference to it [the PL at hand], but in principle – it stays there everything that could occur, but I don't know in this regard ... Can it really happen? Because it says, well it's always there somewhere – yeah, in case you notice other – yeah – notify these -".

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<sup>616</sup> More on the different philosophical interpretations of probabilistic information in the next chapter. See also Gillies, 2000.

# 4, 4: “Precautions. By clinically relevant retarded heart pulsation (Bradychardie)”: “I don’t have it. Or at least I don’t know”.

# 14, 490, ff: “Yes, but this is what I mean – this technical language in there (...) [right] [...] it’s of no use [mhm] (13) {h} *under special condition* (9) {h} What’s a “absorption”? I don’t know. The problem is, yes, - that sometimes I don’t know at all: ‘Am I concerned’? Does this concern me? Because I simply cannot understand, so that then I say, mhm, maybe I have it and I don’t know it yet because I don’t know the technical term?”.

# 2, 4: “*The doctor decides the therapy duration. By rheumatic diseases it can be required the intake of Diclofenac-ratiopharm over a longer time*”: “Whether this is good”.

# 12, Q.61: “*Would you do without the following information paragraphs in the PL? Q. 61: “Why would you do without it?”*”: “Others: ‘hidden side effects’, because you cannot identify them”.

These excerpts present a situation of total prognostic uncertainty on principle. The impossibility to attain the probability assessment tailored to the individual, leads the reader to divergent strategies which not necessarily lead to knowledge updating. Chapter 6 has been devoted to illustrate the probabilistic computation implied by Bayesian updating of personal risk assessment on the basis of PL information. This entails a probabilistic assessment about the eventuality of being concerned by each side effect listed in the PL. The probability of side effect occurrence has been defined as a function of the level of drug toxicity, the quantity (dosage/duration) and the degree of personal sensitivity:

$$P(SE) = P(DT = i/Q = l) \times P(PS = h/ DT = i; Q = l).$$

The corpus was examined as to whether drug consumers indeed venture in a personal risk assessment, and what role PL information plays in this task. It should be noted that in all interviews very little mention is made of PL frequencies as a reference for risk assessment. Precisely, only two readers out of the entire survey sample (n = 55) explicitly refer to the frequency information provided by the PL in order to assess their risk prognosis:

# 12, Q. 54: “*According to the information that you have received from the PL: How probable is that you will be affected by the side-effects of this drug?*”  
“One of them will affect me for sure. ... 0,1% is not little for a lung embolism”.

# 53, 7: she underlies the frequencies in the PL:  
“Many side effects, which I was not aware of, but that only seldom occur”.

PL information is used to know which side effects are possible, rather than to learn how much they are probable. Therefore it represents a source of information about the risk magnitude. Instead the personal probability of being concerned by risk is computed – whenever it is – out of other data, mostly past experience. This might explain why, in the absence of personal experience about the side effects mentioned in the PL, a sense of helplessness overruns the reader in assessing his personal risk prognosis. Especially in the case where the reader was not even aware about the side effect mentioned in the PL, this information produces rather than reduces uncertainty. The probabilistic assessment seems in most cases to be based on an underlying etiological model about the symptom considered.

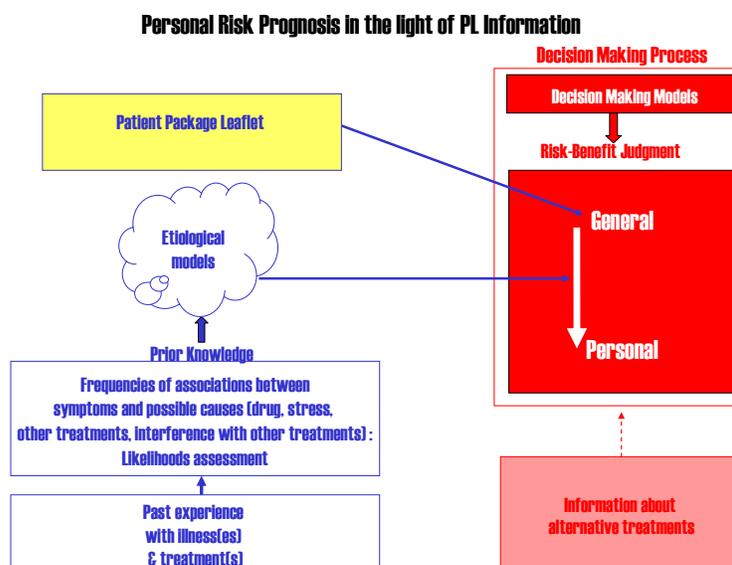
## 4.1 Lay causal models

PL information provides general probabilistic information on drug toxicity and efficacy. These data should be converted into personal assessments.

Many of the responses to open questions and commentaries to the PL indicate that causal models of illness and drug underlie the probabilistic assessment provided in the questionnaire.

Causal information can be derived from past experience (eventually with the aid of other sources of information). Lay causal models can be considered in this framework as the crystallization of accumulated experience over a series of observations.

The role played by causal models in risk prognosis and the assessment of the drug contribution to the occurrence of side effects can be represented as follows:



**Figure 17: The role of etiological models in the assessment of personal risk**

In this model, the integration of general frequency data into a personal risk prognosis is made possible through resort to causal models of illness and drug adverse reactions, which on their turn are based on frequency data coming from past experience.

Causal models detected in the sample vary as for sophistication and solidity: most of the observations manifest categorical judgments of causality (either is the drug responsible for a certain side effect or it is not), however some respondents are less extreme and leave open the possibility of more than one causal factor.

In the former case the causal model is deterministic, in the latter it is probabilistic.

Deterministic models emerging from the corpus contemplate either the absolute exclusion of the drug as the cause of the side effect, or its absolute categorization as a causal contributor:

- the drug is neither sufficient nor necessary for the side effect to occur:  
 $\neg (E \rightarrow D) \ \& \ \neg (D \rightarrow E)$ .

- the drug is identified as the only responsible for side effects: (sufficiency & necessity):  $D \equiv E$ .

When more causal factors are contemplated, then the way is open for a probabilistic modeling of causality: the effect is produced by the drug in concomitance with other factors. In this case the drug can be considered necessary but not sufficient for the effect to occur:  $D \rightarrow E$ , or it can be considered as a sufficient but not necessary cause for the effect to occur (sufficiency):  $E \rightarrow D$ .

The following paragraphs are devoted to illustrate instantiations of these models in the corpus at hand.

#### 4.1.1 Discounting the drug as a possible cause for side effects

In the first model, the drug is excluded from the beginning as a possible cause for the effect under consideration. In general, discounting is the effect of alternative causal attributions: other causes are better candidate for explaining it.

# 4, 10: "*Leukozytenzahlen*. Had it. But something acute. Not in connection with this drug".

# 4, 11: "*Arthritis and muscle pain*. I have every now and then. But I don't believe that it depends on the drug: I had a spinal column surgery ... also before I had it".

# 7, 36: "*Hematoma*. Yes, I tend to have hematoma, but I always did".

# 7, 40: "*Irritability*. Well, which woman is not irritated. That's not a permanent mood".

In all these cases the causal connection between symptom and drug is definitely excluded with no residual doubt.

#### 4.1.2 The drug as the only responsible for side effects.

In the second model, the drug is the only responsible for an eventual side effect. This model is exemplified by participant # 4, who is pretty sure that he will be affected by side-effects in general (Q. 28: score 100): His prognostic probability of being affected by side effects, given that he takes the drug is certain:  $P(E/D) = 1$ . Furthermore he adds as an explanation: "any drug causes side-effects".

In fact this assertion equates to:  $= \neg(D \wedge \neg E) = \neg D \wedge \neg \neg E = \neg D \wedge E = D \rightarrow E$ .

This model fails not only to recognize the fallacy lurking out of the explanation – even if it were true that all drugs have side effects, nevertheless, they do not necessarily affect *all* users – but also identifies the drug as *the* only possible cause for eventual symptoms occurring during the therapy:

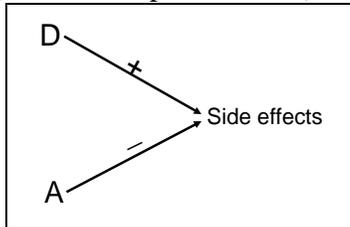
# 2, 5: "*Head-ache*. At least you know the cause of head-aches".

This belief is supported by considerations coming from personal experience: given his healthy past with no disturbances at all, in the case where disturbances occur, he

cannot but think that the cause for them is to be found in the drug. The fact that he cannot think of any alternative cause, induces the participant to think that the drug is indeed “the” cause of side effects. This equates to  $E \rightarrow D$ .

Therefore the underlying causal model should be modelled as the conjunction of both entailments:  $(E \rightarrow D) \wedge (D \rightarrow E) = D \equiv SE$  (the necessity & sufficiency causal model).

Also interviewee #11 clearly identifies the side effects as drug conditioned. Moreover in this case an analgesic (A) accomplishes the task of neutralizing the drug adverse reactions (D). The causal model is consequently articulated into two contributors (a negative and a positive one):



**Figure 18: Positive (Drug) and negative (Analgesic) contributors to a set of side effects.**

The interviewee is able to recognize the weight of the analgesic contribution as adverse reactions neutralizer, by comparing her health condition when she takes both the analgesic and the drug to when she just takes the drug:

Q. 10: Are you satisfied with the drug treatment?  
 (Score: 90): „Well it’s stupid to - [...] at least, and the day after I am also always a little bit run out but- „  
 „Ah, then you notice side effects a little -“  
 „Yes, I do a little – I take Paracetamol here against them“  
 „I take Paracetamol too against – also headaches-“  
 „Yes, yes. When I don’t take it, then I really have head-aches the following day, shivering fit in the night, and I feel very very worn out“.  
 „And this occurs in connection with the drug?“  
 „Yes, yes“.  
 „Unambiguously?“  
 „Yes, This has very strong side effects“.  
 „Long term or only short term side effects?“  
 „Nee, short term, when I take it, then – but I inject it before going to bed and then most of the times I have a quiet night“.

Also interesting is the case where the patient can distinguish between different nuances of the symptom and identify if they are drug conditioned or not:

# 9, Q.30 (positive vs. negative effects ratio: positive)  
 „What side effects do you have with this drug?“  
 „Side effects, it’s sleepiness the day after“.  
 „And do you have to take the treatment regularly? – You sad discontinuously-“  
 „Discontinuously“.  
 „So when you don’t take it, you don’t have this sleepiness?“  
 „Yes“.  
 „So, it’s no doubt the drug?“  
 „Yes“.  
 „Mhm. Are you also able to recognize different sorts of sleepiness?“  
 „Yes“.  
 „And when it is drug conditioned, then you recognize it, that it comes from the treatment“.  
 „Yes, yes, yes, I can recognize it. I also take other drugs, that are lighter, still the day after – doctors say: ,to have the overhang““.

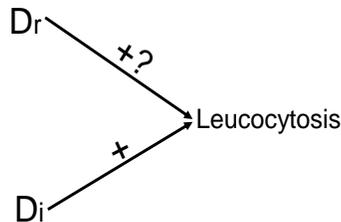
The term sleepiness is here a vague term for different symptoms: A drug conditioned sleepiness, and a normal one, which in the experience of the patient can be recognized as two distinct conditions with related different etiologies.

#### 4.1.3 The drug as a necessary but not sufficient causal factor

In the third model the effect is a product of several conjoint factors, where the drug is considered as one among other equally possible causes. The drug is considered responsible for a side effect, but there is uncertainty as to the amount of this contribution:

# 7: 45: “*Leucocytosis. Yes*”.  
 “*What’s a Leucocytosis?*”  
 “Well, There’s an alteration of leucocytes, well I have many, many more. Normally there are 6000 pro  $\mu$ l Blood, and I have more than 10.000. And they call it already, well above 10.000 they call it Leucocytosis”.  
 “And this depends also on the drug?”  
 “This depends also on the disease, well, the disease as well causes a Leucocytosis, but also this drug produces Leucocytosis. Through that it can also result a hidden effect”.

The ‘hidden effect’ is a formula to express uncertainty as to the extent to which the drug responsibility in contributing to leucocytosis can be “masked” by the disease. The effect might be attributed entirely or mostly to the disease, even if part of it is also due to the drug:

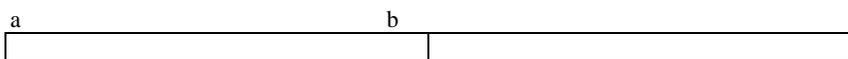


**Figure 19: Joint causation for Leucocytosis: Drug (Dr) as possible and Disease (Di) as certain cause candidate.**

It must be noted that such a diagnostic sophistication is present in only three participants out of 15 in the sample, and among these one can be considered as an almost-expert participant (# 7, a student of alternative medicine).

Fig. 6 illustrates the presence of two alternative causal models as implied by comment #7,34:

# 7, 34: “*Skin. Thinning of the skin. Yes, I have this too, but it may comes also from the long use of creams*”.



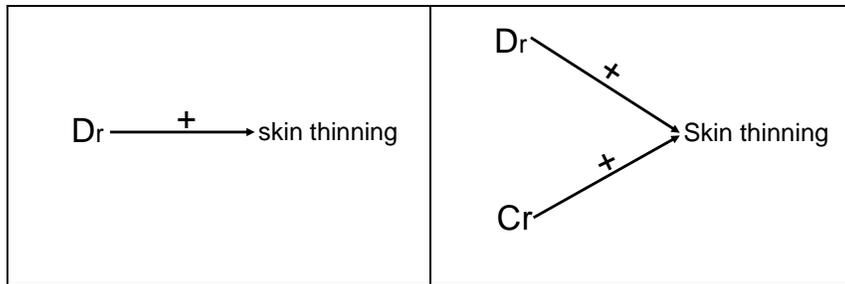


Figure 20: Two alternative etiological models for a side effect: a) single cause model b) joint causes model.

Here two alternative causal models are available and equally plausible. Moreover the second one, which presents two conjoint causes, leaves open the amount of contribution which each single factor brings to the effect. Prognostic uncertainty increases with the number of alternative models, which the subject entertains for the same symptom.

#### 4.1.4 The drug as a sufficient but not necessary causal factor

In the fourth model, the effect can be caused either by the drug or by other causes. As an example we present interviewee #3 and her sight disturbs.

In reading about possible head-aches and sight disturbs associated with the treatments she comments: “I have head-ache every now and then, it can be ...I also have sight-disturbs, but it must not necessary be: I sit all day long before a computer, I wear glasses too ...”.

In this case the etiology is in a certain sense left unsolved: the drug might be the cause for her sight disturbs, but also her short-sightedness and/or the fact that she stays much of the time in front of a computer screen might as well be plausible explanations of her head-aches and sight disturbs.

Narrowing down to the most likely cause or set of conjoint causes and identifying the most plausible one might cost a high cognitive effort and eventually lead to failure because of medical incompetence.

When the causal model is complex, self-efficacy considerations<sup>617</sup> lead the subject to leave the question open if no severe loss is at hand. Here are some other examples (presented once again for the reader’s convenience):

# 4, 9: “*Tiredness*. I am not ‘power-charged’ too, but you can’t say if it depends on the drug”.

# 9, 18: “*And do you notice memory disturbs or don’t you, because it’s also important for our job, an academic job-*”

“I have always had concentration or memory disturbs, but you never know what it is, if it depends on depression, with the anxiety, which compromises also the concentration capacity”.

<sup>617</sup> The concept of self-efficacy refers to the perceived capacity to accomplish a specific task. In this case, with the attainment of the desired level of confidence about the causal attribution. More on this on the next chapter.

# 9, 20: “Occasionally: tiredness. I can’t distinguish, if it comes from the drug or if it is a disease symptom”.

# 15, 6: “Nightmares. This can depend on these tablets”.

In these examples more than one causal model are considered at a time as a plausible explanation for somatic disturbs. If stakes are not high enough, certainty as to the legitimacy of one model rather than the other might be left in “stand-by”.

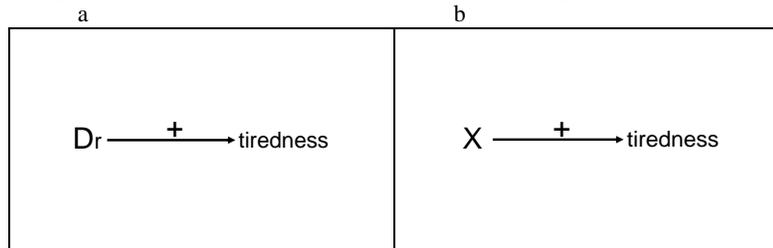


Figure 21: Two alternative etiological models for a side effect: a) the drug; b) other possible causes.

The examples presented so far refer to etiological models for symptoms which the drug consumer has had in the past. It seems that frequency information coming from past observations helps build an etiological model which on its turn plays a determinant role in assessing the prognostic probability that one will be affected by a specific side effect or in estimating the probability that one’s occurring symptoms are originated by the drug rather than by other causes.

Whether causal models can be built out of other information sources other than personal (probabilistic) experience should be deeper investigated. Moreover, it should be also investigated how likelihoods are assessed, i.e. whether an underlying causal model influences the selection of events and therefore contributes to the frequency pattern, or vice-verse or both.

The etiological model might also reveal fallacious:

#10, Q. 20: (Score: 50)

„For instance, when is it difficult to distinguish?“

„Well, when I had this Bronchitis, then I had - through antibiotics, through the first antibiotic treatment - I had rather heavy problems at the stomach, but I thought, that they may come from the mucus, and they probably came from the drug”.

„Did you have them as soon as you took the treatment or not suddenly – how comes that you thought the side effects came from the mucus membrane?“

„That’s my experience. Well, when I had a strong cold, then normally it was like that – first there was some sore-throat and the nose ran, then came cough, and then at a certain point it slid into the stomach. That was my typical cycle, and then by this bronchitis I had the same, but the doctor said to me, no this is, this must be the antibiotic“.

„Alright, when was it simple to distinguish, that it was absolutely a drug side effect“.

„Well, this was of course, that I had experienced it, then I obviously paid a little more attention to it, then I read the PLs“.

„So after a little experience-“

„Yes, precisely, yes“.

„And anyway, in order to be sure that it was a side effect you had to read the PL or-“.

„Yes, whether this – I read PLs more often then, whether it is a possible side effect“.

In this case a consolidated illness model interfere with symptoms interpretation, and therefore needs to be put into question before coming to terms with observational data.

The integration of information from the expert allows for a revision of the causal model.

It is important to note again, that PL is mentioned as a reference document for establishing whether the drug might indeed be the symptom cause in a 0 or 1 fashion, i.e. with little attention to the probability with which symptom and drug are associated.

## 5. The PL as a source of safety information

This study is preponderantly devoted to the analysis of PL information as a source for self-determination information (informed consent). However, the nature of the PL as a modular text, exhibiting all possible negative outcomes, seems more suited to a reference use in case of countermeasures in the face of possible side effects, rather than to a choice support at the beginning of the therapy.

In this context, the reader refers to PL information in order to give a meaning to what he is already experiencing (bodily symptoms).

Indeed the very habit of reading the PL can emerge precisely as a consequence of being affected by adverse reactions.

Overall 60% of the participants declared to always (Score: 100) read the PL when side effects occur.

Two participants have also declared to observe how their body reacts to the treatment and then check if the symptoms might correspond to some of the side effects listed in the PL:

# 9, 15: *“During the treatment with Benzodiazepin and similar chemical entities reactions such as agitation, irritability, aggressiveness, ...can occur, especially by elder patients. I don’t have it, but it was important for me to know that”.*

*“So at the beginning, when you read these side effects, then you simply tried the drug, in order to see, whether these side effects would occur, and then, as they did not occur you went on-”*

*“Yes”*

*“Did you have this ‘trial-attitude’ or-?”*

*“I observed myself”.*

# 17, Q. 66: *“In the PL I read principally... Everything all through and then I observe my body, what concerns me”.*

# 17, Q. 67: *“What function do PL have in your opinion? You can observe yourself and observe the side effects in your body”.*

In the end, the cost/benefit analysis of PL information results in a double balance: A positive balance with respect to PL information as safety information, and a negative estimation determined by the high cognitive costs demanded for using it as a basis for therapeutic decision.

This might be the reason for some skeptical comments:

# 55, Q. 67 (PL function): *„Information about treatments. The patient understands only in part, because one has no idea of the medical special terms. If you read it or not is the same. Either you take it or you let it be. Not all PLs can be precisely understood“.*

# 4, Q. 16 (reliability of information sources):

(PL, TV, Radio: Score: 50): *“They are ok, but they are not tailored to the individual: I already noticed that”.*

# 13, 8: "... The leaflet is not adequate to the target group – The best would be a sort of check list for the patient: 'You shouldn't do this, you should talk about that to the doctor ...'"  
"*You told they are not?*"  
"Adequate to the target group, because you find there information for the doctor, mixed with information for the patients".

## 6. Conclusion

PL information seems to raise more questions than it answers. Generally people perceive it as highly important, but are not in the position to adequately select personally relevant information. This might lead to the overload sensation accounted for through the notion of "relevance paradox". Common heuristics to bypass these shortcomings are reappraisal, counterfactual neglect, idiosyncratic causal models, and uncertainty neglect.

As a result, PL information is not processed in its entirety and is selected through the most diverse filters. This raises some doubts as to its legitimacy as a basis for a personal risk/assessment and to its specific contribution to the consumer's informed consent.

Along these considerations the role of PL in risk estimation might be strongly scaled down.

However, as observed in the last paragraph, PL information has indispensable safety functions, which also the lay reader recognizes.

Rather than being a basis for an evaluation of the treatment choice, the PL is rather conceived as a modular reference text to be consulted at the beginning for precautionary reasons, and then during the therapy in order to identify eventual side effects.



# 9                    **Towards an integrated model of health risk information processing**

*In a world where information is relatively scarce,  
and where problems for decisions are few and simple,  
information is almost always a positive good.  
In a world where attention is a major scarce resource,  
information may be an expensive luxury,  
for it may turn our attention from what is important to what is unimportant.  
We cannot afford to attend to information simply because it is there.*

Herbert Simon, Rationality as process and as product of thought, 1988.

## **1. Introduction**

The main empirical finding emerging from the quantitative study presented in chapter 4 is the observed gap between the increased level of information after reading it on one side, and the lack of any impact on the final decision to take the drug.

The qualitative study has underlined the key role of the information previously received from the doctor during consultation as a selection filter in processing PL information.

This chapter posits the *therapeutic decision* as the teleological determinant for the information processing. Thereby, the therapeutic decision, which is established by the legislator as the communicative purpose of the PL text, suggests the theoretical framework within which the behavior concerning PL information processing can be investigated, namely: decision theory.<sup>618</sup>

The theoretical structure is provided by the Bayesian theory of expected information value. This frame is integrated with the insights gained by cognitive approaches to information processing (“Bounded rationality” theory), and emotional accounts of health risk information processing.

The added value brought about by this integrated model is that it accounts for the accuracy level of PL information processing and impact in consideration of the decision sensitivity to the information at hand.

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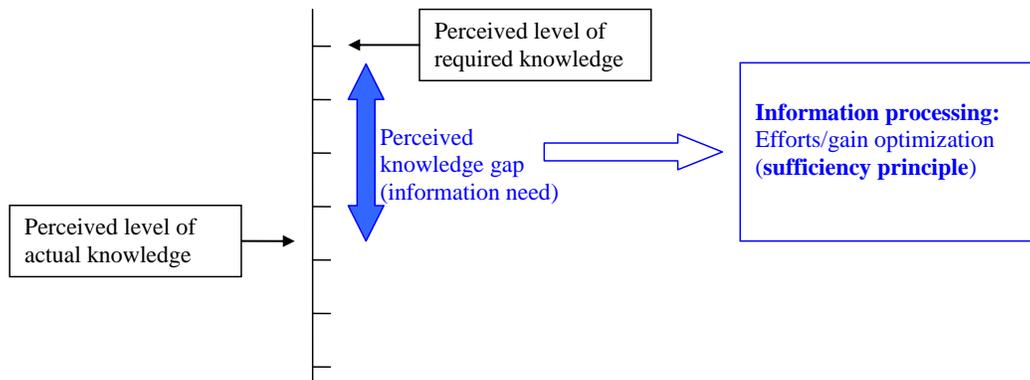
<sup>618</sup> I will consider here only the main parameters of investigation developed in the framework of standard Bayesian theory of decision. Specifically the accuracy of PL information processing will be considered as a function of its expected value to the decision at hand.

The following paragraphs will show that this parameter provide the framework for integrating the diverse phenomena observed in the literature on (health) risk information processing into a unitary model.<sup>619</sup>

## 2. Cognitive accounts of information seeking behavior

More or less explicitly, cognitive literature on information seeking behavior has generally focused on uncertainty (mostly interpreted in terms of perceived information need) as a motivating factor to seek for information.<sup>620</sup>

The principle of sufficiency for instance (Chaiken et al., 1996) assumes that individuals assess their actual level of confidence (AC) and the desired level of confidence (sufficiency threshold: ST) and will search for further information depending on the gap between the two (ST – AC):



The perceived information gap motivates the search for additional information and determines the level of processing accuracy. People will exert whatever efforts are required to attain a ‘sufficient’ degree of confidence, that they have accomplished their processing goals” (Eagly & Chaiken, 1993).

Depending on the efforts exerted in acquiring the information, two modes are generally identified as typical processing modes: the systematic mode and the heuristic mode:<sup>621</sup> “Whether processing goals ... are set high or low influences one of two processing modalities: heuristic and systematic”.<sup>622</sup> A systematic processing is defined by the depth of scrutiny, the quantity of connections and comparisons made, and in general the level of content examination.

Being cognitively less demanding, *the heuristic mode is the default mode* of information processing. Information is in fact normally processed with adherence to the least effort principle, i.e. cursorily and resorting to cues and rules of thumbs as shortcuts to attain the desired amount of data.

<sup>619</sup> As far as recent court decisions let suppose, this part of the work could be profitably used as a reference for the judge, who must evaluate to what extent a specific drug consumer can be deemed responsible for contributory negligence on having failed to take notice of PL information.

<sup>620</sup> See Afifi, Weiner, 2004 for related literature.

<sup>621</sup> See Chaiken et al. 1996, 1989; Trumbo, 1999; Griffin et al. 2002; Kahlor et al. 2003.

<sup>622</sup> Griffin et al. 2002 706.

Individuals can switch back and forth between the two modes within the same task,<sup>623</sup> however they will tend to gravitate more on one or the other based on their capacity to deal with the information, the motivation to invest energy, and time constraints.

## 2.1 Risk information processing

Also the dynamics underlying risk information processing and related fallacies have been explained within a least effort principle paradigm.

To a first wave of studies emphasizing the incapability of lay subjects in dealing with probabilistic information (Kahneman, Slovic, Tversky 1982; Bar-Hillel 1980; Kahneman, Tversky 1982, 1973, 1972; Tversky, Kahneman 1983, 1982, 1974, 1971), an ecologic approach has followed, which has provided an explanatory model for fallacies in probabilistic computation.

Many of these apparent inconsistencies are explained as the result of optimizing processing efforts and heuristic modes of information processing in general (Gigerenzer, 1998, 1996, 1994, Gigerenzer, Hofrage, 1995; Gigerenzer et al. 1999; Cosmides and Tooby, 1996; Kleiter, 1994, Kohler, 1996; Giroto, Gonzales, 2001; Reyna et al. 2003;).

It seems indeed that a variance of information processing strategies has emerged in empirical research as for the interpretation of risk information: both rational learning and biases are found to characterize risk information impact on perceived risk.

Along a Bayesian approach to the impact of risk information on precautionary behavior, Viscusi et al. could establish that “Consumers responded in a manner that was broadly consistent with the main predictions of an economic model of rational safety-related actions” (p. 81): rational learning implies in their model that prior risk over- or underestimation are corrected by frequency information (p. 62-64). Nevertheless other studies report about divergences in decision, which were not consistent with the difference in probabilities between the decision sets.<sup>624</sup>

In Smith, Desvouges, and Freeman’s (1985) study about consumer willingness to avoid risks from hazardous wastes, it results that subjects attach a higher marginal valuation to risk reduction in case of low-probability accidents than to higher probability ones, showing thereby to treat lower probabilities as equivalent to higher ones.

Several theoretical arguments have been put forward to explain what has been identified as a low probability bias: Magat, Viscusi, Huber (1987) argue that people try to simplify their processing costs by taking into consideration only one of the two main risk components, namely either probability or magnitude:

“By focusing on either the magnitude of the loss or the probability of its occurrence and ignoring the second characteristic, they tend either to overreact to the risky event or to ignore it. If people have difficulty internalizing low probabilities but are *forced* by a survey to consider them in making decisions, they may respond by mentally augmenting the probability to a familiar level. In contrast, if decision-makers are allowed to ignore low-probability events, as in

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<sup>623</sup> Trumbo, 1999: 392; Kahlor et al. 2003: 356.

<sup>624</sup> See Magat, Viscusi, Huber, 1987: 90ff.

making actual flood insurance decisions, they may do so in order to simplify the processing costs of making those decisions” (p.91).

A possible alternative explanation could also be that under a certain threshold all frequencies are considered equivalent and a difference in risk probability does no longer translate in an analogous (not even marginal) difference in risk perception: the stochastic meaning of  $10^{-6}$  and  $10^{-7}$  might make no difference to the perception of risk. *Thus findings about the tendency to overstate true probabilities could be explained by the level of granularity with which frequencies are estimated.* This hypothesis can be confirmed by another study of Magat, Viscusi, Huber (1987) about job risk perception with larger risk probabilities, where no evidence of overreaction has emerged, and on the other hand by studies where extremely low probabilities, no matter how small, didn't prevent the subjects to perceive the risk, as long as the mere possibility still constituted a threaten.<sup>625</sup> In fact “thinking about low probability events imposes considerable demands on individuals' cognitive capabilities” (p. 97) and one might hypothesize that under a certain threshold the very process of figuring them out more precisely than needed might be not worth undertaking.

The relationship between cost/benefit estimation and degree of processing accuracy seems to underlie the dynamics related to risk information. However, in the specific health setting contradictory reactions to risk information have been observed (from active information seeking to information avoidance) which cannot be exhaustively explained by the least-effort principle.

### **3. Perceived desirability of health risk information**

Information about side effects is generally considered very important among drug consumers: when asked, 90% of patients express desire to receive information on side effects, which they consider the most important aspect of drug information (McGavock 1998). Furthermore, information about adverse drug reaction is among the highest ranked when compared to other pieces of information related to the therapy (van Grootheest et al. 2004; Laaksonen et. Al. 2002; Bouvy et al. 2002; Åström et al. 2000; Howard et al. 1999; Vigilante, Wogalter 1997). Moreover, risk issues are the most recurring concerns when evaluating drugs (Kare, Kucukarslan, Birdwell 1996).<sup>626</sup>

But, on the other hand, in a study on Intrinsic Desire for Information (IDI; Åstrom et al. 2000) a correlation between IDI low scores and anxiety was observed, either coped with by trusting the health professional or by predominantly looking for

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<sup>625</sup> SOURCE ... In contrast, Kunreuther et al. (1978) found that for catastrophic events probabilities are so low that their possible outcome tends to be ignored.

<sup>626</sup> Indeed discontinuation of drug treatment as a reaction to development of side effects, occurs particularly in cases when no information on side effects has been given by the practitioner (Enlund et al. 1991). This means that confidence in the health professional and in his decision is not shaken when the drug consumer knows that side effects are “part of the bargain” and are under control.

In fact satisfaction with the information received has been found to affect adherence (O' Brien et al. 1990; Coulter et al. 1999).

reassuring information (see table 1). The intrinsic desire for health information (factor 1) was distinguished from the expressed desire of information (factor 2) in order to account for inhibition in information request. The subgroups emerging from factor 2 were obtained through a qualitative analysis of open answers: no expressed desire; expressed desire but no expressed purpose; expression of both desire and purpose. IDI high scorers tended to express desire of factual information in order to make an autonomous judgment, instead low scorers tended to seek for reassuring information or to avoid information and rather rely in the health professional as a delegate for decision.

	<i>No expressed desire for information</i>	<i>A desire for information, but no expressed purpose</i>	<i>A desire for information, and an expressed purpose</i>
<b>High score</b>	No real interest in further information	Specific interest in side effects, expected benefits and interactions with other drugs.	Specific interest in side effects, safety issues and general effects of drugs, including benefits. Desire to keep control of my 'body'. <u>Wanted choices and information about alternatives.</u>
<b>Low score</b>	Lack of interest in information; information provokes <u>anxiety</u> ; rather <u>trust decision of HPs.</u>	Main interest in reason for drug and how to take it. Want <u>reassurance on benefit if drug</u> , but <u>willing to put trust in HPs. Decisions</u>	Want <u>reasons for drug choice and reassurance of benefit</u> . Feel they should know what they are taking.

**Table 11 Qualitative results of a study on Intrinsic Desire for Information (IDI). Source: Åstrom et al. 2000.**

In general, low scorers were more concentrated on benefit information, whereas high scorers were interested in data about the risk associated to the treatment and eventual alternatives (p. 161-162).

Previous work of the same group has shown that providing information about medicines to patient who desires it makes them more satisfied and empowered, whilst providing the same information to those who do not want it makes them more anxious and less empowered (Duggan, Bates 2000).

Laaksonen, Duggan, Bates (2002) have found information seeking attitudes to be positively related to *past experience with side effects*, but further research is needed to establish the causality direction: it might be that more information leads to more awareness and therefore to side effects perception when they occur, or else the reverse. In fact low scorers were evasive about adverse drug reactions and not sure about their being correlated with the drug. Moreover, high scorers were not only aware of side effects but also of the drug being helpful: "It's about a balance between the good and bad effects", while low scorers manifested the tendency to take the medicine for duty and to lack any information need: "I just don't know if knowing will help ... I mean, a bad effect is a bad effect."

*What emerges from these studies is that information insufficiency and the desirability of health information do not necessarily associate.* The perceived knowledge gap and the desire to become knowledgeable about health risks do not necessarily go hand in hand.

### 3.1 Emotional elements in processing risk information

The empirical findings emerging from studies on risk information seeking behavior show a discrepancy between the information need predicted by the gap between actual level and required level of knowledge for confident judgment/decision and the perceived desirability of further information. Indeed, cognitive and socio-psychological research has addressed the message type and personality dimensions as relevant aspects of information seeking behavior.<sup>627</sup>

In general four main strategies have been identified among concerned people addressed by sources of risk:<sup>628</sup>

1. Seek relevant information;
2. Avoid relevant information;
3. Reappraise the situation;
4. Seek for counterbalancing reassuring information.

1. Relevant information seeking is the normative behavior, which is however constrained by cost considerations.

2. Avoiding relevant information can be a reasonable strategy either when it is considered too costly, or when it is perceived unhelpful, *because things can hardly be changed*.

For instance, it has been reported that 57% of individuals with hereditary risk of colon cancer declined an offer for genetic testing.<sup>629</sup> Sometimes the perception arises, that more information does not resolve the problem.<sup>630</sup>

3. In the cases where risk is perceived as *unavoidable* and therefore no active countermeasure can be taken, coping strategies can be activated which reduce the anxiety level by reappraising the perceived menace.

Reappraisal is a common phenomenon in situations where risk is characterized by lack of control. The impossibility to act against it induces the subject to act on his emotions and reevaluate the threatening source thereby reducing its perceived danger. As a consequence, risk perception decreases *and also perceived information need*.<sup>631</sup>

Witte (1998) assumes that this ostrich's policy is a consequence of low efficacy in relation to a threat. In this sort of situation the subject "*ignores the threat and recommended responses and instead engages in coping responses to reduce fear*".<sup>632</sup> This "perceptual defense" typically manifests in the individuals "distort[ing] or ignor[ing] any incoming information about a threat".<sup>633</sup>

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<sup>627</sup> See Bealheaves, Long, 1999 and related literature.

<sup>628</sup> Afifi, Weiner, 2004: 181.

<sup>629</sup> Lerman et al. 1999.

<sup>630</sup> Babrow, 2001:563, cited in Afifi, Weiner, 2004.

<sup>631</sup> Afifi, Weiner, 2004: 181 ff.; Preuss, S, 1986: 74 ff.

<sup>632</sup> Witte, 1998: 437, cited in Afifi, Weiner, 2004: 182.

<sup>633</sup> Witte, 1998: 438, cited in Afifi, Weiner, 2004: 182.



is: ‘Is there any serious risk if I change?’, if the answer is negative, the agent opts for the first salient alternative and unconflicted change occurs.

With a moderate level of stress, the decision maker is motivated to switch to a vigilant information processing mode (VIP). However it is emphasized that, given time and other resources constraints, this is the exception rather than the rule.

*As the level of stress increases, emotional response modes, rather than rational ones are activated.* Especially if the risk is perceived as unavoidable, the subject faces the decision situation either by procrastinating and through reappraisal of the perceived risk, or by making ‘panicked choices’. Also Connolly has reported with regard to high risk, that it “seems to produce either paralysis or catastrophe for the layperson (manager, consumer, parent or whatever) – paralysis, from contemplating the insolubility of the problem; catastrophe, from acting without awareness”.<sup>637</sup>

*Balneaves’ account of health risk information processing explicitly takes into account the decision context as a determinant factor for the coping strategy adopted, rather than tracing it back exclusively to personality factors.*

This differentiates their approach from the cognitive account of risk information processing, in that it makes explicit the role of the decision context in determining the extent to which further information is desirable.

In fact, with respect to risk perception and related anxiety, risk information can generate four types of effect, depending on whether it increases/decreases uncertainty about the risk:

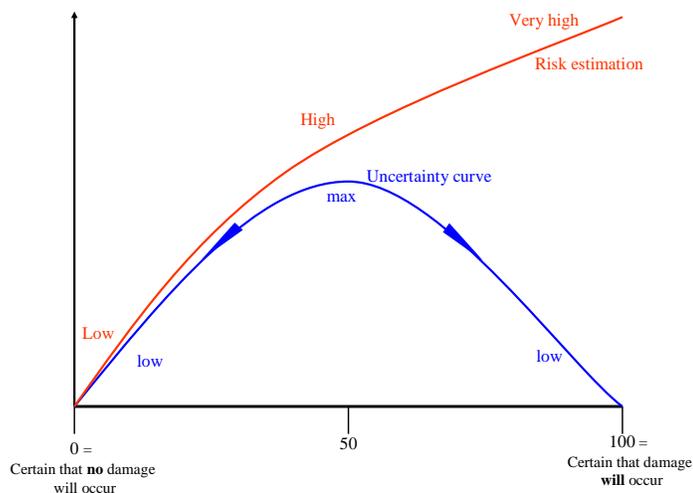
	Increase uncertainty		Decrease uncertainty	
risk	0 → .5	1 → .5	.5 → 0	.5 → 1
anxiety	increase	decrease	decrease	increase

In a scale between 0 and 100, the highest prognostic uncertainty is in the middle (.5): this is where you would not bet for either of the possibilities. At 0 you are certain that damage will not happen. At 100 you are certain of the contrary.

If you esteem a risk at 50 before reading the PL, and at 70 afterwards, your prognostic uncertainty concerning it has decreased, because you are more confident than before, that indeed it will occur, but your perceived risk has increased. The diagram shows this double effect:

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<sup>637</sup> Connolly, 1980: 70.



**Figure 22: Risk perception curve and the uncertainty curve in comparison: a decrease in uncertainty can lead to lower or higher health risk perception, depending on whether it confirms or disconfirms side effect occurrence.**

The more obvious (Bayesian) strategy for reducing prognostic uncertainty would be to collect further information in the hope to decrease it.

However, this strategy could induce in the health setting to an even higher anxiety level, which explains why reactions to health risk information are so idiosyncratic.

Reduced prognostic uncertainty related to risk information can in fact either lead to greater confidence about safety or, on the contrary, to the certainty of damage.

If risk estimation increases then, depending on factors such as perceived control and capacity to process information, the above mentioned strategies are activated, which are not necessarily congruent with rational learning.

*In the end, when things can hardly be changed, no benefit can be expected from further information, apart from a useless additional dose of anxiety.*

The uncertainty “scissor” can explain why information eventually leading to uncertainty decrease about “bad outcomes” is not always welcome.

*This means that the desirability of further information not only depends from its epistemic contribution to uncertainty reduction, but also from the decision context, i.e. from the potentiality that the decision can be changed by the expected information.*

The categories developed within the Bayesian account of the expected value of information to decision can help identify the distinct aspects which contribute to the estimation of its expected impact on the decision, and therefore possible antecedents for the degree of accuracy with which it is processed.

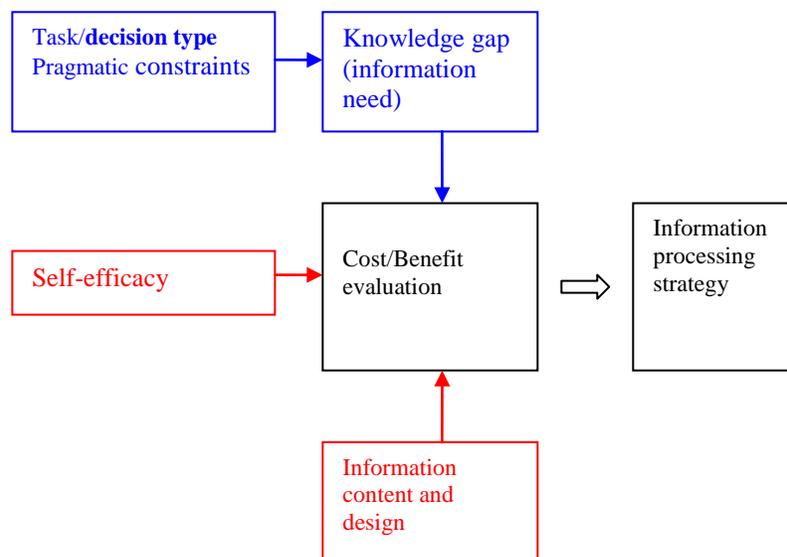
#### 4. Information and decision

The integration of cognitive and context factors (the decision at hand) in the explanation of information processing strategies traces back to Herbert Simon and its coinage of the concept of “bounded rationality”.<sup>638</sup>

Bounded rationality theories explain processing accuracy through an articulated set of factors the most salient of which are:

1. the task at hand (stakes involved, decision type, time and other pragmatic constraints),
2. and the perceived capacity to gather and process relevant information to accomplish it: self efficacy.<sup>639</sup>

These factors integrate in the estimated benefit/cost of information processing, and therefore indirectly influence the degree of its accuracy:



The task at hand, with its perceived importance and the stakes at issue, determine the perceived knowledge gap: this predicts the level of perceived benefit of further information. The estimation of processing costs depends from self efficacy and the content and design of the information support.

The difference of this model with respect to the sufficiency principle approaches is that here the decision situation and its pragmatic constraints (time, resources) plays a determinant role in the assessment of the information need.

<sup>638</sup> Simon, 1982. The distinction between the Bayesian computation of optimal sample size, and the sufficiency principle can be best illustrated by recurring to Simon’s distinction between “optimizing” and “satisficing” analyses. In the former type, the correct point to terminate information is found by equating marginal costs of search with expected marginal improvement of alternatives. In the latter type, search terminates when the best offer exceeds an aspiration level that itself adjusts gradually to the value of the offers received so far. Simon, 1988: 67, 69.

<sup>639</sup> See Kahlor et al. 2003; Reyna et al. 2003; Dougherty et al. 2003; Martignon and Krauss, 2003, Schneider Schanteau, 2003; Griffin et al. 2002; Gigerenzer, 2001; Slovic, McMackin, 2000; Gigerenzer et al. 1999; Trumbo, 1999.

In particular for risk information, psychological literature has underlined the relationship between perceived benefit of risk information, perceived risk, and actual information processing: subjects are likely to ignore information, if they feel it has high costs relative to its benefits, and are unlikely to seek out and process risk information if they perceive little risk (Bettman, Payne, Staelin, 1987).

*The explicit reference to the decision context helps explain the different attitudes towards health risk information better than the mere consideration of the perceived uncertainty.*

Specifically, the parameters determining the value of information *to a decision*, build a structure where emotional, cognitive, and contextual factors integrate and provide a comprehensive account of health risk information processing. These parameters are presented in the next paragraph and then applied to the specific case of PL information.

#### **4.1 Expected value of information to a decision**

In the Bayesian theory, the *information value* is established by its expected contribution to decision optimization: this contribution is measured as the difference between the expected reward under the current state of knowledge, and the expected reward brought about by the act that would be chosen on the basis of the expected information.

The value of further information to decision will therefore depend not only from its epistemic contribution (belief change), but also from its capacity to reverse the decision and thereby bring a higher reward. This capacity is a relational property which depends from the information impact on the probability distribution and from the decision sensitivity to this epistemic change.

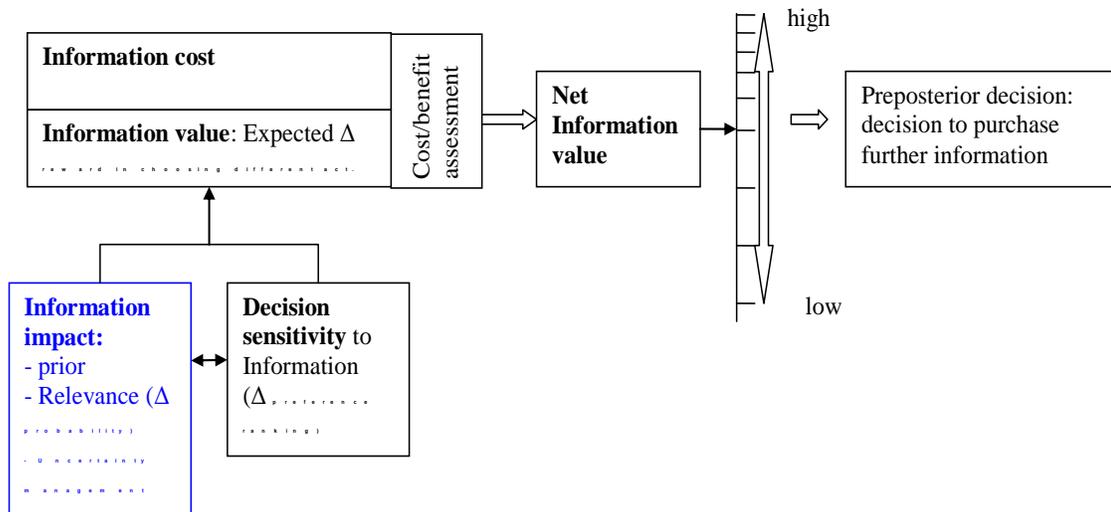
The decision sensitivity to potential changes in the probability distribution of the states of the world is strictly connected to the utility matrix.

The closer the different payoffs are in the preference ranking, the more sensitive is the decision to even slight changes in probability assessments, vice versa, the higher the differences in the expected payoffs connected to the different acts, the greater must be the change in probability distribution in order to affect the decision. The information capacity to change the decision will depend on whether the posterior probability distribution balances the preference ordering so as to alter the acts ranking

From the point of view of decision change, the effect of information is categorical: either does it change the decision or not. However, depending on the anticipation that the expected information could indeed lead to a decision change, than its value is measured out of the difference between the expected rewards under the current choice, and the payoff brought about by the act that would be chosen under the new state of knowledge.

The decision to acquire further information, “preposterior decision”, will depend on its expected value to the decision, and on its estimated cost (economic or cognitive).

The diagram shows the fundamental components contributing to the expected impact of the information to decision change, and the eventual decision to acquire it.



**Figure 23: Fundamental dimensions determining the impact of information on a decision and the related decision to acquire it (preposterior decision).**

The net information value is a relational dimension which depends on the expected value of the information to decision optimization and on the cost of acquiring it. On its turn, the expected value of information depends both on the expected impact of information on the agent’s belief and on the decision sensitivity to this change. The information impact is a function of the prior state of knowledge, the difference between the prior and posterior probability distribution – information relevance – and in the increase or decrease in uncertainty.<sup>640</sup> The Bayesian analysis of the expected net gain of information to decision defines the expected gain of information not simply in terms of uncertainty reduction, but in terms of its effective contribution to decision change. The value of information depends in this framework not only on its epistemic input, but also on the extent to which the decision can be improved by it.

#### 4.2 Decision sensitivity to new information

In the decision context, belief change produces a modification of the probability distribution assigned to the relevant states. The new distribution can lead to a decision change to the extent that it favors a different act. Therefore, the contribution brought about by a piece of information within a decision context *entails but exceeds its epistemic impact*. In fact, belief change is a necessary but not sufficient condition for decision change. In order for an agent to change his opinion about the best act to choose, the decision itself must be *sensitive* to this information.

<sup>640</sup> For a detailed account of the computation of the net gain of information see Winkler, 1972.

The value of hypothetical information to decision is therefore strictly connected to the payoffs related to each act-state pair: only information which changes the preference ordering of the acts can be said to have a value for the decision.

Let's consider again the example of the decision matrix concerning the week-end out.<sup>641</sup> Note that utilities differ from the matrix presented in chapter 6, because here the decision maker is really looking for a week-end in the nature with outdoors activities, so that the other alternatives are just a makeshift solution, because neither museums nor the crazy crowd are your favorite Sunday's pastime. But of course a picnic in the rain is not the best you can wish. So, considering your optimistic estimations about the weather ( $s_1$  = good weather,  $s_2$  = variable weather,  $s_3$  = rainy weather), this is the hypothetical decision matrix:

	$S_1 (.45)$	$S_2 (.35)$	$S_3 (.20)$
$a_1$ picnic	Outcome <sub>11</sub> 100	Outcome <sub>12</sub> 90	Outcome <sub>13</sub> -100
$a_2$ big-town-sightseeing	Outcome <sub>21</sub> - 100	Outcome <sub>22</sub> 50	Outcome <sub>23</sub> 0
$a_3$ museum	Outcome <sub>31</sub> - 100	Outcome <sub>32</sub> 25	Outcome <sub>33</sub> 30

Here your strong preference for outdoor activities can be evinced from gap in utilities distribution between  $a_1$  and  $a_2, a_3$ .<sup>642</sup>

The expected utilities for each single act are:  $a_1$ : .335;  $a_2$ : .130;  $a_3$ : - .3035.

In this case, given your strong preference for nature and quiet, *only a strong change in the states probability distribution can lead you to change your decision*. With a moderate weather forecast which predicts sunny weather with probability .10, variable weather with probability .70, and rainy weather with .20 probability, the new expected payoffs for each act are:  $a_1$ : .53;  $a_2$ : .25;  $a_3$ : .13. Therefore  $a_1$  would be again the optimal act.

Only a much more pessimistic weather forecast would be able to change your mind. If storm is predicted with probability .85, unsettled weather with probability .10 and good weather only for a tiny .05, your decision matrix would rather look like that.<sup>643</sup>

	$S_1 (.05)$	$S_2 (.10)$	$S_3 (.85)$
$a_1$ picnic	Outcome <sub>11</sub> .05	Outcome <sub>12</sub> .09	Outcome <sub>13</sub> -.85
$a_2$ big town	Outcome <sub>21</sub> -.05	Outcome <sub>22</sub> .05	Outcome <sub>23</sub> 0
$a_3$ museum	Outcome <sub>31</sub> -.05	Outcome <sub>32</sub> .025	Outcome <sub>33</sub> .25

The expected payoffs for each act are:  $a_1$ : - .71;  $a_2$ : 0;  $a_3$ : .25. Therefore the optimal act would be this time  $a_3$ : going to the museum.

<sup>641</sup> See chapter 6 § 1.2

<sup>642</sup> The difference in utilities distribution between  $a_1$  and  $a_2, a_3$  requires an equally strong unbalance in the probability distribution of possible states in order to change the outcomes preference order.

<sup>643</sup> The payoffs in the cells are already weighted by related probabilities in order to ease the appraisal of the effect produced by the probability distribution on outcomes ranking.

The decision sensitivity and expected information impact are fundamental dimensions in the estimation of information value. This has on its turn dramatic consequences in the preposterior decision of purchasing further information or else being content with the current state of knowledge. An application of these considerations to the perceived value of PL information will help us integrate the diverse phenomena observed in the empirical studies and in previous research with regards to health information seeking behavior and PL information processing.

## **5. An integrated model of health risk information processing**

Antecedents for information seeking behavior have been generally identified in perceived uncertainty and knowledge gap mediated by cost considerations (which in cognitive terms depend on the level of text readability on one side and on self-efficacy, health literacy, education and demographic data on the other).

Discrepancy between the uncertainty possibly perceived by the subject and information avoidance or low desire of further information have been traced back to emotional aspects underlying the health choice: cognitive dissonance, reappraisal strategies. Balneaves and Long account however allows tracing back these strategies to the decision type faced by the individual: ultimately it is the expected impact of the information on the decision change rather than its uncertainty decrease potential which determines whether this information will be valuable for the individual.

Information will profit from systematic processing whenever it is considered valuable for a better decision. *Whenever no alternative is at sight, the cost of acquiring it is considered worthless.* Also when it is perceived as useful, but too demanding in terms of information design in relation to one's own processing capacities it tends to be dismissed.

Bayesian decision theory provides in this sense a "reductionist" explanatory model for reappraisal, in that the decision to avoid information is explained by the relatively *little reward of acquiring new information when there is little hope that the information will make a difference.*

The disentanglement of uncertainty reduction from the impact on the decision allows accounting for the idiosyncratic coping strategies registered in the literature about health risk information processing.

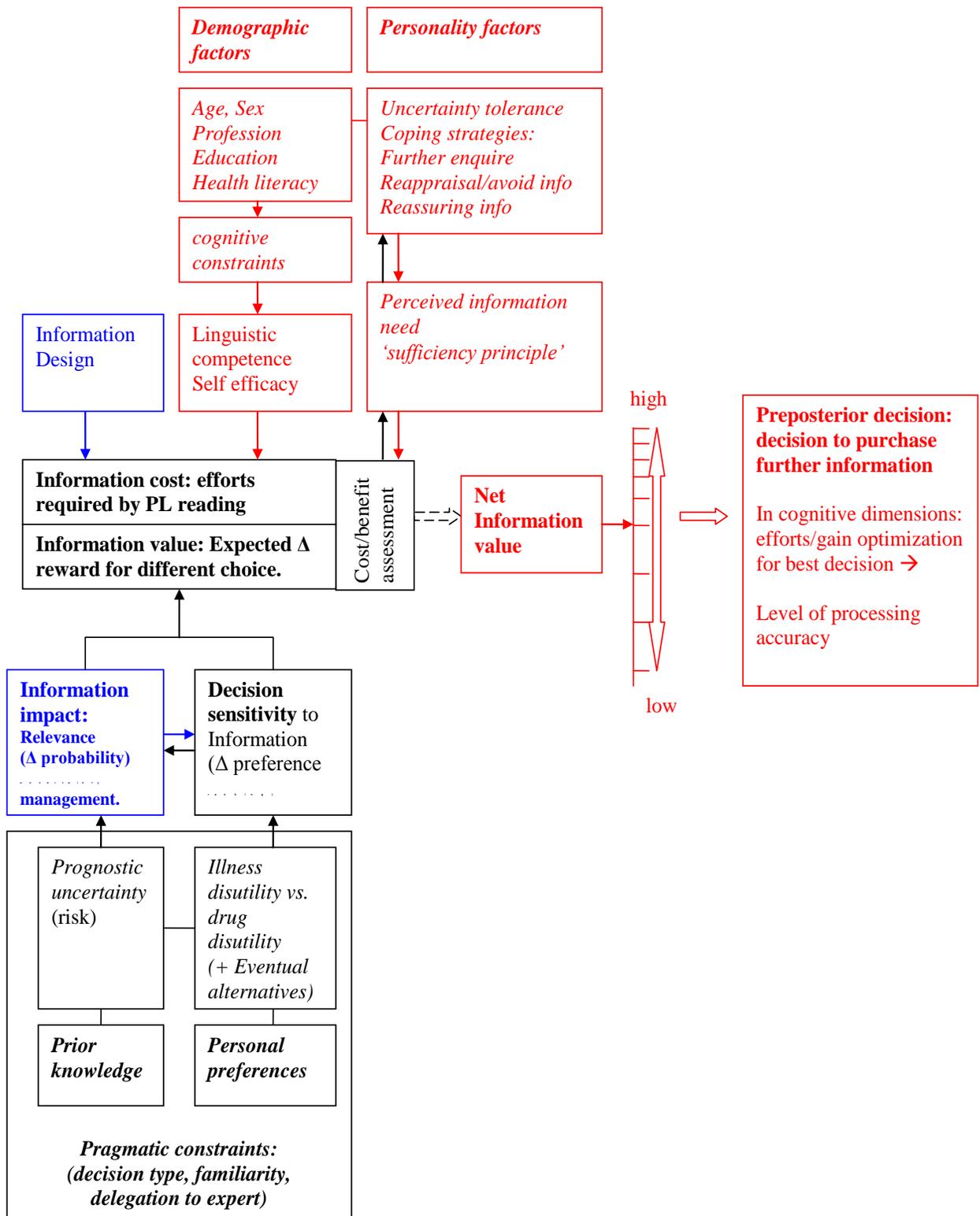


Figure 24: Pragmatic and cognitive constraints related to therapeutic information management. Bayesian categories such as estimated decision impact through belief change ( $\Delta P$ ) and change in preference ranking are integrated with personality factors such as uncertainty tolerance and self efficacy, and contextual aspects related to decision types.

The diagram shows that the information seeking behavior is determined by the expected information value as postulated by Bayesian theory. This not only depends from the level of uncertainty as normally assumed by cognitive theories of information processing, but from the decision sensitivity to incoming information.

The least effort principle is accounted for in the diagram by considering cognitive costs of processing determined by:

1. the information design: cryptic language and generally low readability heightens the cost of information processing, and therefore decreases its net value;
2. (health) literacy level and code competences of the reader.

*Therefore, in this domain, health literacy, in addition to linguistic competence is a fundamental factor in the decision to process risk information.* Self-efficacy, the perceived capacity to process the information at hand, does also influence the cost estimation of information processing.

Coping strategies adopted towards this kind of information are not solely dependent on personality factors but ultimately depend from the cost/benefit assessment which bases on expected net gain of information to decision. Therefore reappraisal strategies are considered to be the combination of the subject's demographic/psychological profile and of the constraints determined by the decision (e.g. lack of alternatives).

When applied to the analysis of PL information processing, this model can be considered a valid starting point for capturing relevant parameters determining its impact on the consumer's decision:

1. expected cost of processing PL information – determined both by the information design and by the subject's level of (health) literacy;
2. expected net gain of processing this information – determined by the expected value of this information to the decision in relation to the decision sensitivity to it;

The results provided by the survey presented in chapter 7 provide evidence that the therapeutic decision made with the doctor is hardly shaken by PL information, even when this information is declared to have brought a positive contribution in terms of knowledge. The qualitative study show that doctor's information also functions as a filtering key for coming to terms with information overload and the relevance paradox.

This suggests that decision sensitivity to PL information is strongly influenced by reliance on the doctor, and that a promising field of future research is the investigation of knowledge integration from different sources of information with diverse reliability and tailoredness factors.

## **6. Summary and conclusion**

This chapter has presented a theoretical account of the contradictory attitudes towards health risk information observed empirically.

Cognitive theories of information seeking behavior and psychological accounts of health risk information processing have been presented and integrated into the Bayesian approach to the analysis of information value.

Cognitive theories of information seeking behavior posit the uncertainty derived from a perceived knowledge gap as the motivating factor determining the search for further information and the degree of processing accuracy.

Theories of “Bounded rationality” emphasize the task at hand as the factor which determines the level of knowledge required, and therefore the perceived information gap. Within these theories, the “satisficing” level, where no need for further information is required, is determined by the decision at hand. This specification distinguishes the mere epistemic value of information from its contribution to decision change.

Balneaves’ account of the different coping strategies to health information processing indeed explicitly considers the decision as the context within which different processing strategies are activated, depending on the decision maker’s faculty to avert the risk through more information.

An explicit and articulated account of the relationship between information and decision is offered by the Bayesian analysis of the expected net gain of information, where the information value is analyzed not only in terms of its epistemic relevance, but also by taking into account the *decision sensitivity* to the information.

The integrated Bayesian model of health risk information processing accounts for the apparent contradictions observed in the empirical literature by tracing emotional reactions back to the decision characteristics (decision sensitivity to the expected information) and to the perceived capacity to deal with the expected information and use it to improve the decision.

The integrated Bayesian-cognitive model implies for instance that whenever no alternative is at sight, the cost of acquiring further information is considered worthless. Also when information is perceived as useful, but too demanding in terms of information design in relation to one’s own processing capacities it tends to be neglected.

By applying the Bayesian instrumentation to the analysis of the expected value of PL information, the model identifies relevant parameters which contribute to the perceived expected value of PL information, and therefore to the degree of accuracy with which it is processed. The degree of accuracy depends on a cost/benefit estimation which, on the benefit side considers the epistemic contribution brought about by PL information in terms both of uncertainty reduction (information relevance), and in terms of the decision sensitivity to the expected information.



## 10 Conclusion and outlook

This research has undertaken the task to evaluate PL information within its legal setting in the attempt to bring a contribution to the debate on its role as a basis for informed consent.

The resulting claim is that PL information cannot totally dispense the pharmaceutical firm from taking on responsibility for relevant residual risk, in that this information cannot be considered adequate for consent to be valid.

The argumentation is articulated in three parts:

- I. A legal analysis of PL information;
- II. A normative evaluation of PL information;
- III. An empirical research on the impact of PL information on the therapeutic decision.

### I

Notwithstanding the official qualification of PL information as product instruction within safety regulation, liability norms related to the distribution of residual risk translate it in a risk disclaimer in analogy to the information provided by the doctor within the institute of informed consent.

Therefore two main legal functions can be identified for PL information:

1. warning and risk prevention function, in observance of the consumer's right to safety;
2. disclosure of residual risk, in observance of the constitutionally protected right to self-determination.

The notion of residual risk is fundamental in this setting (chapter 1), because it is the risk which the beneficiary party needs to shoulder unless he has not previously been *informed* about it by the doctor and/or by the pharmaceutical firm.

In fact, safety information should prevent avoidable risk to occur; instead self-determination information should declare the unavoidable risk, so as to insure that

the drug user is aware of it when he decides whether to undertake the therapy or not.

Because disclosure of residual risk is also performed by the doctor, two preliminary steps were needed in order to evaluate the communication role of PLs in this framework:

- 2.1. the analysis of risk disclosure within the institute of informed consent (chapter 3);
- 2.2. the analysis of the responsibility spheres regarding the information of residual risk (chapter 4);

Within point 2.1 two issues have been touched:

The repercussions of the 2<sup>nd</sup> Amendment Law for Compensation on doctor-patient communication;

The communicative status of therapeutic information under the tort and the contract liability regime respectively.

2.1.1 Through the amendment of § 253 Abs. 2 BGB and the abolishment of § 847 BGB, the 2nd Amendment Law of Compensation extends compensation for moral damages (damage for pain and sufferings) – which were previously limited by § 847 BGB to torts – to breaches of contract.

This has important consequences for the doctor-patient communication. In fact, under tort liability, compensation is only granted when a causal nexus can be established between damage and failure to provide adequate information. The right to choice is not protected *per se*, in that compensation is granted not for the lack of information but for the physical damage.

For instance, lack of information about alternative therapies, which do not essentially differ from the proposed procedure in their risk/benefit profile, does not lead to tort liability in that the damage would not have been less probable if the patient would have chosen one of these alternatives.

This setting models the doctor-patient communication as a risk transfer transaction rather than as a counseling relationship, where information for decision is a value *per se*.

The counseling relationship is precisely fostered by the extension of compensation duties for moral damages also to contract liability. In fact, within this framework information about therapy and alternatives is due to the patient not as a legitimization of bodily intrusion, but as a consequence of the asymmetric relationship to the patient and therefore as part of his professional duty. Compensation is granted also for the simple violation of the right to self-determination independently of health damage.

2.1.2 In the informed consent model entailed by the tort liability regime, doctor patient communication serves the purpose of legitimizing the medical procedure. In the counseling model inherent to contract liability, communication should enable freedom of choice. Consequently, the reason for which the patient shoulders the

risks connected to the therapy differ in the two settings: in the IC model, the patient is supposed to shoulder the risks connected to the procedure *because, having being informed about them, he is aware of them*; in the counseling model, rather than merely consenting to a proposal, the patient *actively participates in the decision*, and shoulders eventual damages because he takes on co-responsibility for the medical treatment, and bears the risks which do not fall under the medical control.

The point of this discussion was to evaluate the communication model fostered by tort liability in comparison to contract liability and thereby identify the communicative status of PL information. In fact, given that liability for product instruction faults falls under tort liability (chapter 2), PL information ends up to conform to the IC model of therapeutic information and thereby to serve the purpose of residual risk reallocation. This task qualifies it as a risk disclaimer with the additional drawback that no comparative data about therapeutic alternatives are given.

2.2 The analysis of the responsibility spheres leads to following conclusions:

Consent to the doctor equates to a global approval to therapy. However, the doctor's information duty does not include all possible residual risks, but only those considered relevant for the patient's decision. Detailed information, which cannot and need not be disclosed by the doctor is also part of the consent and is provided by the PL. By taking the drug, the consumer accepts also the risks enlisted in the PL warnings and not mentioned during consultation.

Whenever damage follows, which do not result from prescription errors, and the mention of which was not part of doctor's professional duties, the patient has no right to compensation, if they are included in PL information.

From this it results that, the residual risk disclosed in the PL and which is not part of the doctor's information duties, totally falls on the patient's shoulders.

## II

Once it has been established that PL information is not only a means of safety protection, but also part of the therapeutic informed consent, the point is then to evaluate whether PL information can be considered adequate for consent to be "informed", i.e. valid.

1. *Prima facie* objections to this claim are:

1.1. *Lack of timeliness of PL information.* PL information comes on principle too late, when consent has already been given to the doctor. A solution to this problem has been proposed by Koyuncu with his bi-phased model: preliminary consent to the doctor, conclusive consent through drug intake.

1.2. *Possible conflict between the doctor's and the patient's risk/benefit assessment made on the basis of PL information.* If the PL brings an autonomous element to patient's decision, than it should do it by providing him with a different basis for

choice than that provided by the doctor (risk/benefit assessment). This brings a contradiction within the decision process: either should the patient rely on the doctor's risk/benefit assessment; or else make a personal risk/benefit assessment on the basis of PL information, perhaps also different from the doctor's one.

*1.3. Absolute lack of information about alternatives.* If consent to doctor has been given with little or no knowledge of alternatives, consent to PL is given exclusively with information related to the prescribed product. As Wolz puts it: „When the user has it [PL] in his hands, than a decision about a specific treatment has already been made. Alternative drugs are not available or only with difficulty, so that often the decision reduces to a choice between taking this pharmaceutical product or not ... *Even optimal designed PLs cannot warrant the user an adequate ground for decision*”.<sup>644</sup>

*1.4. “Non-tailoredness” of PL information.* PL information grounds on a toxicological-statistical concept of risk, which needs to be integrated with the patient's personal data on the basis of the doctor's tailored evaluation of therapeutic risk. Therefore the PL cannot substitute the doctor as a source for self-determination information, in that the principle of self-determination requires that the individual is made knowledgeable of *his personal* risk/benefit profile, whereas product information is necessary general and abstract.<sup>645</sup> A decision can be considered autonomous, only if made on the basis of personally relevant information.<sup>646</sup>

*1.5. Risk information overload and lay incompetence to discern personally relevant from irrelevant information.* In general it can be said that given the high preponderance of risk information<sup>647</sup> in relation to data about benefit, any decision-maker should decide not to take the drug. The main difficulties lie indeed in selecting the items of information which are personally relevant and material to the decision. This can be a source of paralyzing uncertainty or non-compliance, when it does not lead to the general refusal of PL information.<sup>648</sup>

*1.6. Risk assessment uncertainty* due not only to incomprehensibility, but to a general incapacity to understand the health implications related to the information items contained in the PL.

These points touch epistemological aspects of PL information as a basis for knowledge updating, risk/benefit assessment and therapeutic decision.

Therefore the evaluation of PL information has gone beyond its linguistic and communicative aspects (chapter 5) and has investigated the role of PL information in the therapeutic decision within the framework of Bayesian theory, which is the

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<sup>644</sup> Wolz, 1988: 15, 16: “Hat der Verbraucher erst einmal in der Hand, so ist die Entscheidung für ein bestimmtes Medikament bereits gefallen. Alternativpräparate werden nicht oder nur unter Schwierigkeiten erreichbar sein, so das oft nur die Entscheidung zwischen Einnahme und Nichteinnahme dieses Arzneimittels bleibt ... Auch inhaltlich optimal gestaltete Gebrauchsinformationen garantieren also nicht den Entscheidungsspielraums des Verbrauchers”.

<sup>645</sup> See Hart, 2003: 605; Krudop-Scholz, 2005: 156. See also Stöhr, 2006: 148.

<sup>646</sup> “Selbstbestimmt ist die Entscheidung dann, wenn die aus der Sicht des Patienten entscheidungsrelevanten Informationen zur Verfügung stehen”.

<sup>647</sup> There are PLs with more than 80 side-effects: Grandt et al., 2005: 511.

<sup>648</sup> See Krudop-Scholz, 2005: 159-162.

theory developed for the analysis of the relationship between information and decisions under uncertainty, such as therapeutic decisions typically are (chapter 6).

2. The normative analysis has demonstrated the substantial incapacity of PL information to provide a solid contribution to the lay autonomous decision.

PL information can in general provide a basis for assessing the drug toxicity and efficacy in general, however its epistemological and therefore predictive value *for the single user* is very difficult to specify.

The doctor's task is precisely to combine both knowledge of the drug and of the patient in order to predict the risk level to which the patient is exposed to by taking the drug.

PL information about side effects rather represents the hypotheses to be confirmed, than the answer to them: Each side effect mentioned in the list raises the question as to its possible occurrence, a question which the probabilistic data associated to it only marginally help answer.

This is a fundamental objection to the *legitimization of this instrument as a valuable basis for informed consent*.

### III

The empirical part of the work consists of a quantitative study (a survey with  $n = 55$  sample size), and a think aloud experiment ( $n = 15$ ). Participants for both studies were recruited among drug consumers with the aim to investigate the role of PL information in their therapeutic decision.

1. The survey was designed as a paired comparisons test, where participants were asked to give their risk and benefit assessments about the drug before and after reading the PL (chapter 7).

The main result deriving from this study is the gap between increased perceived level of information and

3. insignificant PL impact on benefit and risk assessments;
4. absolute no impact on the decision.

The presence of a specific topic of concern seems to have some effect on the degree of confidence in choice and on the personal benefit assessment before reading the PL. In the post-PL phase the persistence or emergence of a specific topic of concern is associated with lower degree of confidence in choice, less favourable risk/benefit assessment, lower benefit assessment (both general and personal), and higher desire to further enquire about the drug.

However, the presence of a specific topic of concern seems to have no influence on the final decision which remains as definite as before (100 score for all participants).

Considering the generally positive evaluation of PL information and the increased perceived level of information after PL reading, these data support the hypothesis that the therapeutic decision concerning prescription drugs is quite insensitive to PL information. The concept of decision sensitivity to incoming information can indeed

provide an explanatory framework for the discrepancy between increased level of knowledge after PL reading and lack of impact on the therapeutic decision.

2. The qualitative study (chapter 8) investigates the dynamics underlying PL information selection and processing. In general a certain reluctance to read the entire text has been observed in the sample. On the other side, PL information is perceived as highly important. This schizophrenic attitude has been explained by the relevance paradox phenomenon: any piece of items contained in it has virtually extreme importance and cannot be done away unless one feels justified in neglecting it for some reason. On the other hand the probability that all the items of information will jointly concern the reader is extremely low. Indeed only a minor proportion of the information items do refer to the special health condition in which the reader finds himself. This leads the single user to consider the text as *constitutively over-informative*.

Information filtering is mainly performed by drawing on the knowledge acquired through doctor's consultation, but also reappraisal strategies, uncertainty neglect and cognitive dissonance selection play an important role in explaining information seeking/avoidance in the health setting in general and in relation to PL information in particular.

This raises some doubts as to the legitimacy of PL information as a risk disclaimer also on empirical grounds.

However, as observed in the last paragraph, PL information has indispensable safety functions, which also the lay reader recognizes.

Rather than being a basis for an evaluation of the treatment choice, the PL is rather conceived as a modular reference text to be consulted at the beginning for precautionary reasons, and then during the therapy in order to identify eventual side effects.

3. The last chapter is devoted to integrate the phenomena observed in the empirical studies and in the literature previously devoted to the topic in a unitary model based on the Bayesian analysis of the expected value of information to decision. This framework provides the basis for tracing cognitive and emotional accounts of risk learning behavior back to the least effort principle (as already advanced by Bounded Rationality theories) and to the concept of decision sensitivity.

At the end of this investigation, some suggestions for improvements are proposed to the legislator and the text designer.

### **1. Suggestions for the legislator**

The contribution of PL information within the institute of informed consent should be more clearly defined.

This demands an examination of the concept of autonomous decision in the health context, and a definition of the PL binding force on the basis of its actual contribution to autonomy rights. Following questions could guide the discussion:

- 1) The institute of “informed consent” should protect the right to self-determination and autonomous choice: does the communication model fostered by it really warrant these rights?
- 2) What is an autonomous choice at all? What does the autonomous choice of a lay decision maker in a highly specialist sector consist of? Is it at all possible?
- 3) If yes, does PL information provide an independent contribution to the information provided by the doctor?
- 4) Does the liability setting determined by the institute of informed consent correspond to the real responsibilities ascribable to the stakeholders involved in therapeutic decision making (pharmaceutical firm, doctor, drug consumer)?

The regulation of pharmaceutical risk communication in particular and medical risk disclosure in general should take into account these issues in an interdisciplinary perspective. Precisely, it is proposed to analyze the communicative nature of medical risk information by integrating legal concepts with categories devised by communication theories and decision theory.

A possible consequence of this examination could be the partial disentanglement of PL risk disclosure from risk responsibility reallocation. Flexible legal tools are needed in order to account for the specific risk inherent to drug usage.

Patient’s responsibility should be therefore articulated as follows:

- The patient’s contributory liability for damage caused by non-compliance to safety instructions should be maintained. Indeed along the analysis proposed in the thesis, this sort of information can be validly used by drug consumers for averting or minimizing risk.
- Instead PL information cannot be considered adequate for consent to be valid. Therefore it cannot offload the pharmaceutical firm from the responsibility related to residual drug risk, whenever the doctor cannot be considered liable for it. For some types of adverse drug reactions, it could be suggested, that pharmaceutical firm takes on damage liability, even if declared in the PL and do not exceed the tolerability threshold but can be considered relevant. As a consequence strict liability of pharmaceutical firms should be extended to damage which is below the tolerance threshold level, but which is nevertheless relevant for the damaged person.

These claims can be also supported by the consideration that damage liability is only a monetary compensation for injuries which touch high valued goods such as psychophysical wellbeing.

Liability threshold lowering from intolerable to relevant damage should not be felt as a punitive measure, but rather as an incentive for the overall system, so that more “virtuous” enterprises are not damaged by unfair concurrence of reckless ones.

Moreover, given the declared low incidence of adverse reactions in comparison to market turn-over, this would not constitute a severe economic loss for pharmaceutical companies – at least not comparable to the loss suffered by the user. From the perspective of law steering functions, an extension of pharmaceutical strict liability would increment efforts towards a more systematic approach towards safety research within pharmaceutical research innovation.

A “damage warranty” would on the other side greatly contribute to the restoration of the reputation and image loss suffered by firms on the wave of pharmaceutical injuries.

To the patient’s responsibility should instead be ascribed the duty to check consistency of doctor’s with PL information, and to control if some important information should be delivered to the doctor before taking the drug, in consideration of the safety instructions contained in the PL: hypersensitivity to components about which the doctor is not aware; interference with drugs, of which the doctor might have no knowledge, etc. up to the verification of dosage correspondence.

This task corresponds to the cooperation duty entailed by the doctor-patient reciprocal contractual obligations.

More generally, with an explicit separation of the safety and self-determination aspects related to PL information, patient’s contributory negligence in safety issues could be more clearly emphasized and contribute to balance the distribution of responsibilities around drug consumption.

## **2. Proposals for text improvement**

1. In addition to the uncertainty generated by the probabilistic assessment of side effects occurrence, also the disutility associated to each of them is difficult to evaluate for the lay user. This is mainly due to the incompetence perceived by the lay reader in appraising the importance of the drug effects mentioned in the PL.

There is widespread opinion which considers PL texts overwhelming and redundant. The relevance paradox shows that this overload sensation would be overcome precisely by adding explanatory information, rather than reducing its volume. A description of the health implications and importance of side effects and symptoms should be provided. This “indexing” procedure would constitute a valuable interpretation key for selecting information and appraising the risk magnitude. This would also promote compliance, when this is caused by over-alarm.

2. Furthermore, countermeasures should be associated to each side-effect as exemplified below:

Transitory side effect → keep on with the therapy;

Important side effect → call the doctor;

Severe side effect → stop the therapy and call for the doctor;

Severe to fatal side effect → stop the therapy, emergency measures are required, go to hospital immediately.

3. Iconic – eventually standardized – signs could beneficially accompany the verbal text.

4. Finally, more transparency on the communication point in general (prohibition, advice, precaution, disclosure of unavoidable risks, countermeasures to side effects,

etc.) would certainly contribute to enhance PL comprehensibility and applicability. This is eased by letting the grammatical form adhere to the substance of the message (instructions and prohibitions in imperative form, risk disclosure in assertive form) and by avoiding to connect messages which bear underlying opposite presuppositions or implications.<sup>649</sup>

Also the avoidance of redundancies and an improved textual design as recommended by the EU readability guidelines would significantly enhance PL readability and user-friendliness.

Notwithstanding communication improvements, there is a limit to patient friendliness though: it is the limit imposed by the margin of risk which is inherent in drug use itself. However comprehensible and well designed no package leaflet could cancel the uncertainty induced by information about side effects.

In this perspective, the role of PL information as a distributor of responsibility about residual risk should be reconsidered in the light of the observations presented in this research.

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<sup>649</sup> See chapter 5 and 9 for some examples.



# Appendix



## Survey method and demographic data

### 1. Information impact

The information impact was measured by the difference between risk/benefit assessment before (pre) and after reading the PL (post). These questions elicit responses as to the magnitude and probability of risks as well as to the expected benefit both in general and in personal terms:

#### Benefit assessment

Q. 24 (pre PL)/ Q. 50 (post PL): <b>General</b> benefit prognosis:	“How much effect do you ascribe to this drug in comparison to alternative treatments for the same disease?”
Q. 25 (pre PL)/ Q. 51 (post PL): <b>Personal</b> benefit prognosis:	“How much effect will the drug produce on you?”

#### Risk assessment

Q. 26 (pre PL)/ Q. 52 (post PL): Drug toxicity (side effects severity):	“Do you think that this drug has <u>severe</u> side-effects in comparison to alternative treatments for the same disease?”
Q. 27(pre PL)/ Q. 53 (post PL): Drug toxicity (side effects quantity):	“Do you think that this drug has <u>many</u> side-effects in comparison to alternative treatments for the same disease?”
Q. 28 (pre PL)/ Q. 54 (post PL): <b>Personal</b> risk perception (chance of being affected by side effects):	“How probable do you judge the eventuality of being affected by the side-effects of this drug?”

#### Benefit-risk assessment

Q. 30 (pre PL)/ Q. 56 (post PL): Benefit-risk assessment: positive?	“Do you think that the positive effects of this drug are greater than eventual side-effects?”
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#### Benefit-risk odds

Q. (pre PL)/ Q. 58 (post PL):

The subject is asked to give his personal benefit-risk assessment within a sum-estimation (positive and negative) adding up to 100. The format is shown below:

<b>Positive effects</b>		<b>Side effects</b>			
	+		=	100	

In order to assess whether PL information is integrated with old knowledge deriving from experience with drugs and illnesses, a series of questions eliciting one’s own amount of experience have been included in the first part of the questionnaire:

#### Experience

Q. 6: Experience with the drug at hand	“Are you taking this drug for the first time?”
Q. 18: Experience with drug in general	“How much experience do you have with drugs?”
Q. 19: Past positive reaction to drug treatments	“When it comes to you drug are ... effective” (from never to always in 100 point scale)
Q. 22-22: Past negative reactions to drug treatments	“I had side-effects in the past when I took a drug” (from never to always in 100 point scale)

The intent of these questions was not only to test “lay bayesianism”, but also to investigate the relation between PL information impact and previously hold experience. In the case of pharmaceutical products in fact, familiarity does not

necessary mean greater amount of knowledge (for instance about long-term health implications). However, familiarity with a product might induce an artificial sense of acquaintance with it and traduce in a low need for information.

## 2. Expected value of information to decision

In order to establish the expected value of information in this context, a battery of questions was proposed to the participant as to assess his degree in decision confidence, his perceived information level, and the expected relevance of further information to decision (all answers should be given in the form of a 0 to 100 assessment).

- Q. 10: "Are you satisfied with the treatment choice?"
- Q. 11: "How much information do you have on the treatment?"
- Q. 12: "Is there anything that makes you uncertain?" (Yes/No answer)
- Q. 13: "What about?" (Open answer).

Furthermore, the expected value of information in terms of *informativeness* (extent to which further information may reduce uncertainty) and *promise* (probability that expected information will result in a different decision)<sup>650</sup> have been tested through questions 14 and 15:

- Q. 14: "Could an eventual clarification about it eliminate the uncertainty?"
- Q. 15: "Are you considering not taking the treatment because of eventual missing information?"

Level of concern (therapy motivation) has been tested through a counterfactual question:

- Q. 9: "What would be the consequence of not taking the treatment?"

## 3. PL declared value

The perceived value of PL information has been also addressed by direct evaluation questions:

- 39. I find the information included in this PL (From "Not at all": 0 to "Definitely Yes": 100):
  - a. sufficient;
  - b. already known;
  - c. excessive;
  - d. disquieting;
  - e. useful;
  - f. other.

Furthermore, the desire to introduce additional information in the PL after reading it was elicited, together with questions related to PL information behavior:

- 58. Would you let insert further information in the PL? (From "Not at all": 0 to "Definitely yes": 100).

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<sup>650</sup> See Hammit, 1999.

59. How important would be this further information? (From “not important at all”: 0 to “very important”: 100).
- How the treatment functions in my body;
  - Probability of treatment success;
  - Other.
60. Would you do without the following information paragraphs in the PL? (From “Do not do without” to “Do without”: 100).
- Chemical components;
  - Indications;
  - Warnings;
  - Duration and doses;
  - Others.
61. Why would you do without it? (Open question).

Now a couple of questions about your reading habits:

62. I read Patient Package Inserts ... (From “Never”: 0 to “Always”: 100).  
I read the Patient Package Insert ... (From “Never”: 0 to “Always”: 100):
63. Before beginning the therapy.
64. Just when adverse reactions occur.
65. I read the whole text.
66. In the PL I read principally ... (Open question).
67. What kind of function/functions do PPI have in you opinion? (Open question).

#### 4. Decision delegation

The most important parameter in this setting is represented by the reliance in the doctor who prescribed the drug.

As stated above, information seeking behavior in a decision context is predicted by the degree of uncertainty in the choice to be made. In an expert-to-lay domain this uncertainty might be endemic and therefore different strategies may be devised in order to avoid the costly task of acquiring information which is difficult to understand: even when the form itself is comprehensible, nonetheless many doubts may be left as to the interpretation of the health implications that some messages bear. By delegating the decision to an agent, the layperson not only avoids the task of computing a risk-benefit assessment, but can also be confident that the expert, being in possess of all relevant information, can make a better decision than he.

Therefore only the conjunction of motivation, self-efficacy, and *uncertainty about the expert decision* can induce the layperson embark in the possibly frustrating task of trying to make a personal assessment of benefit and risks in a certain health decision.

The extent to which the choice was delegated to the physician is captured by question 17, which enquires how the drug choice has been made. Responses range from simple prescription to discussion of alternatives.

Trust in the expert is measured in question 16 (reliability of several information sources).

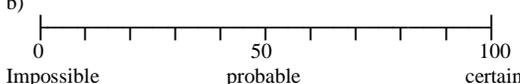
#### Methods of analysis

The tests have been carried out with non-parametric methods (Kruskal Wallis test, Kendall Tau). Paired samples t-tests and t-test for independent samples have also been used for comparing means differences of dichotomic variables, when parameter distributions approached normality.

## 5. Judgment elicitation

The elicitation of probability judgments is itself a branch of decision theory (drawing its methodological tools on psychometrics: a discipline devoted to measuring subjective perceptions of physical qualities such as sound or light intensity).<sup>651</sup> Extensive experimentation has led to a wide spectrum of elicitation techniques and vivacious debates about the most appropriate methodologies for probability elicitation from experts or decision makers. In sum, Edwards and Winterfeldt list three major methods: direct numerical estimation, procedures based on equality judgments among events with known and unknown probabilities, and gambles (based on the expected value assumption: e.g. scoring rules).<sup>652</sup>

Although direct elicitation is considered to be the less reliable among the three, still it is the only one feasible in a survey context. All answers relating to probability and value estimations were formulated in a quantitative fashion:

How probable do you think is the eventuality of being affected by the side-effects of this drug?	
a) I cannot judge it.	b) 

Also recent contributions in risk communication studies have made use of direct numerical estimation in survey questionnaires (Trumbo, 1999; Kahlor et al. 2003).

## 6. PL classification

The impact of the information should obviously be measured along the data provided by the PL to each drug user. Therefore package leaflets have been classified according to the quantity of risk information delivered, and to its potential impact.

The side effects were subdivided in three groups:

1. definitely light;
2. definitely severe;
3. 'Indefinite' cases with following uncertainty sources:
  - d) uncertain implications of the symptoms (clinical-labor tests and blood serum modifications included);
  - e) medical jargon;
  - f) semantic aspects;
  - g) pragmatic aspects.

<sup>651</sup> See for an introduction Yates, 1990.

<sup>652</sup> Edwards, von Winterfeldt, 1986: 118 ff.

## 6.1 Definitely light and definitely severe side effects

Whenever the word “vorübergehend” (transitory) accompanied the description of a symptom, this was considered as definitely light. Examples are typical stomach-ache, constipation, etc.

When a clear indication was given, that the symptoms mentioned would last only during the therapy, then they were classified as “light”:

“Störung der Blutbildung, die jedoch nach der Behandlung wieder verschwinden”  
 (“Blood count modifications, that however disappears after the treatment”).

Also the opposite holds: when the adjectives “schwer” (severe), “gefährlich” (dangerous), “lebensbedrohlich” (life threatening), and “tödlich” (fatal), “chronisch” (chronic) appeared as word modifier, the effect was classified as severe. Severe cases were considered also those side-effects, where an indication of interrupting the therapy was given:

“Sollten die genannten Symptome auftreten oder sich verschlimmern, so müssen Sie Diclac Dispers absetzen und sofort Kontakt mit Ihrem Arzt aufnehmen”  
 („In case the mentioned symptoms occur or worsen, you must interrupt the therapy with Diclac Dispers and put yourself in contact with your doctor immediately”).

„Wenn Sie glauben, dass eine solche Reaktion bei Ihnen vorliegt ... beenden Sie die Einnahme von CoAprovel, und suchen Sie sofort ärztliche Hilfe“ (CoAprovel –Sanofi).  
 („If you believe that these reactions occur to you ... Stop to take COAprovel and look immediately for the help of a health professional“).

Therefore the same side-effect was classified as indefinite or severe/light according to the way it was presented: “Darmentzündung” (intestines inflammation) without any further explanation was classified as ‘indefinite’ because of the difficulty for the patient to assess the health implications linked to the disturb (transitory and negligible? Or severe disease?), but whenever a modifier could help the reader assess the severity of its health implication, then the side-effect was classified accordingly: “Chronische Darmentzündung”: severe side-effect.

Sometimes short explanations may accompany the disease name: Propycil 50 (Admeda) for instance, adds to the side-effects list an explanation of “Lupus erythematoses”, “Periarteriitis nodosa” and “Coombs test”. In these cases the description might provide a cue as to the health implications related to the illness, and therefore the cases were considered accordingly.

## 6.2 Indefinite side effects

When clear severity indexes are missing, and the symptoms described are not familiar to the reader, then uncertainty as to their importance and health implications arises. The following points are intended to display some of the difficulties the reader might

be faced with in assessing the risk magnitude, when reading a specific side-effect in the warning list:

a) The greatest uncertainty source is represented by the description of symptoms whose (eventual long term) implications might not be clear for the reader. This leads to misunderstandings in both directions: light side-effects might unduly alarm the reader, because he draws false conclusions from their description, or vice versa, he might erroneously neglect severe side-effects and consider them as negligible (eventually failing to take adequate measures timely).

The classification considered these cases as indefinite, not because of their possible objective consequences, but because they are neither presented as clearly light nor as severe, and also not as “medium” adverse reactions.

Also difficult to gauge for a lay reader is the meaning of a labor test result concerning blood values (blood particles, sugar level, and lever values) or clinical kidney tests. The medical implications of such data are not part of his competence and therefore uncertainty might arise as to their interpretation. The same holds for information concerning changes in cardio-circular system.<sup>653</sup>

b) A second source of uncertainty is medical jargon.

c) On a semantic level, many symptoms are described which are not to be considered side-effects in themselves, but which are rather alarming signs of more dangerous disturbs:

„Zeichen einer Nierenerkrankung bis zum Nierenversagen:

Verminderung der Harnausscheidung, Ansammlung von Wasser im Körper (Ödeme), allgemeines Unwohlsein

(“Signs of kidney disease up to kidney failure:

Urine decrease, water retention (edema), general indisposition” - Followed by the instruction to stop the therapy”

Unfortunately these symptoms are not always presented as such in a cluster which identify them as a consequence of a common cause, but rather singularly and without any seemingly relevant relation to each other. Signs of disturbs linked to the drug have been counted themselves as side-effects if no overarching framework linked them to a common underlying disturb. Otherwise, they have been subsumed under the side-effect of which they are symptoms.

‘Scope ambiguity’ also disorients the reader as to the interpretation of determinants:

“Sollten *die genannten* Krankheitszeichen auftreten oder sich verschlimmern, setzen Sie Dioflenac-ratiopharm 74 SL ab und nehmen Sie sofort Kontakt mit einem Arzt auf”.

---

<sup>653</sup> In fact in some texts these side-effects are explicitly presented as concerning the physician’s diagnostics:

“Darüber hinaus kann ihr Arzt EKG-Veränderungen sowie Herzrhythmusstörungen feststellen”;

(„Moreover, your physician can diagnose ECG-modifications and heart rhythmus disturbs as well“);

“Ihr Arzt kann eine abnormal Anhäufung von Stoffen im Lungengewebe (pulmonale Infiltrate) feststellen”;

(Your physician can diagnose an abnormal accumulation of material in the lung tissues [lung infiltrates]).

“In case the mentioned illness signs occur or worsen, interrupt the therapy with Dioflenac-ratiopharm 74 SL and contact a doctor immediately”).

The text remains ambiguous as to the scope of the determinant (“die genannten”, the mentioned) over the preceding list: all of them or just the last paragraph?

d) Another source of uncertainty lies on a higher order level of text comprehension, namely the pragmatic conversation maxims. From the point of view of illocutionary commitment, there are several cases of “attenuated” warnings: Text passages, in which the PL formulae provide a peace of risk information with no clear illocutionary meaning.

All cases falling under the points a-d have been classified as ‘indefinite’.

PL themselves were rated according to the number of light, severe and indefinite side-effects listed in the warnings. Although taken into account in the coding phase, frequency was not considered during the analysis, because it resulted to be a redundant dimension in ranking the PLs (i.e. PLs with higher numbers of side effects had also the most severe plus the most common).

## 7. Topics of concern

The 9 topics of concern emerged *through PL reading* information are the following:

### Topics of uncertainty after reading the PL

	DRUG/ILLNESS	UNCERTAINTY ITEM AFTER READING THE PL	Δ RISK
# 1	Atorvastatin/High cholesterol	Hair loss	+ 10 (odds)
# 6	Iodides/Hypo-thyroid	High blood pressure	- 45 (odds)
# 7	Prednisolon/Arthritis	Difficulties in assessing optimal individual dosage	0
# 8	Antibiotics/Post-OP therapy	Information overload	+ 70 (SE severity)
# 14	Antibiotics/Skin infection	Ulcerous colitis	+ 10 (SE quantity); + 35 (SE severity).
# 15	Mirtazapin/Depression	Epilepsy	+ 5 (personal risk)
# 17	Phenprocoumon/Thrombosis prevention	Side effects in general	0
# 38	Tetrazepam/Lumbago	“It helps alleviate your pain, but it cannot remove the spasticity”	+15 (odds) + 30 (SE severity)
# 47	Phenazon eardrops/Light ear infection	Dosage	+10 (odds)

**Table 12: Cases of no uncertainty before reading the PL, and uncertainty afterwards.**

### Topics of uncertainty before and after reading the PL

	DRUG/ ILLNESS	UNCERTAINTY ITEM BEFORE PL	UNCERTAINTY ITEM AFTER PL	Δ RISK
# 2	Diclofenac/ Rheumatic pains	Side effects	Long term side effects	+ 20 (SE quantity) + 20 (odds)
# 9	Benzodiazepn/ Depression	Dependency	Dependency and long term effects	+ 30 (SE quantity) +10 (SE severity)
# 10	Cortisone spray/ Cold	Cortison	No cortisone information	+ 10 (personal risk)

# 12	Antibiotics/ Respiratory tract infection	Side effects	Tendinitis. I would like to ask the doctor - I know that normally drugs have side effects, but I would like to know whether the situation gets worse if I take it again (increased personal sensitivity through repeated treatments).	+10 (SE quantity)
# 13	Phenprocoumon/ Thrombosis prevention	Therapy duration	Skin necrosis. Control of lever values. Nervus femoralis: what is that?	+10 (SE quantity) + 10 (personal risk)
# 27	Anti-histamines/ Seasonal allergy	The chemical entity means nothing to me	Whether the level of tiredness could be lower as it is by me. And whether it comes from the illness or from the drug.	+ 10 (SE quantity) +10 (SE severity)
# 32	Potassium –magnesium/ Heart attack prevention	Eventual side effects	Relationship with homeopathic therapy. Why did the doctor not simply prescribe magnesium?	+ 10 (personal risk)
# 34	Antibiotics/ Vaginal infection	Dosage and interference with other drugs	Dosage and therapy duration. Resistance.	+20 (SE quantity) +20 (personal risk) +50 (SE severity)
# 35	Diclofenac/Articulation inflammation	Drug efficacy	Little perspective of a speedy recovery	+ 30 (SE severity) +10 (odds)
# 41	ACE inhibitor / High blood pressure	Hydration precautions during therapy	Hydration and loss of salts. How often should check ups (blood and so on) be carried out by the doctor?	+20 (SE quantity) +30 (personal risk) +70 (SE severity)
# 42	Nitrendipin/ High blood pressure	Side effects, for instance dizziness and tiredness	The special dosage of the treatment.	- 20
# 44	Homeopathic drug/ Fungal infection	Enough efficacy?	Enough efficacy?	0
# 50	Thyroid/ Hypothyroid	Side effects	Interferences with other drugs. Some words unknown.	+15 (personal risk) +2 (SE severity)

### Topics of uncertainty before reading the PL (and absent afterwards)

CASE	DRUG/ILLNESS	UNCERTAINTY ITEM BEFORE READING THE PL	Δ RISK
# 3	Pill/menstruation regulation	Risks and side effects: for instance thrombosis	+ 20 (SE quantity) + 20 (odds)
# 11	Interferon beta/Multiple sclerosis	I notice that I get haematomas but it is not so bad.	+ 30 (SE quantity) +10 (SE severity)
# 29	Tetrazepam/lumbago	Do also respiratory muscles get relaxed? This would be bad.	+ 10 (personal risk)
# 39	Antibiotics/vesica inflammation	Resistance in the long term	+10 (SE quantity)
# 55	Biphosphonate (etidronic acid)/ osteoporosis	The drug was prescribed in a different dosage than in the package	+ 10 (SE quantity) +10 (SE severity)

## Wissenschaftliche Studie über Beipackzettel von Medikamenten

Liebe Befragte, lieber Befragter,

Sie haben diesen Fragebogen in Ihrer Arztpraxis oder bei Ihrem Apotheker bekommen, weil Sie zurzeit mit einem verschreibungspflichtigen Medikament behandelt werden. Dieser Fragebogen behandelt, wie Packungsbeilagen verstanden werden. Durch Ihre Mithilfe tragen Sie zu deren Verbesserung bei.

Dieses Projekt ist eine Zusammenarbeit der Universität Bielefeld und der Universität Lugano. Die Daten werden innerhalb einer Doktorarbeit ausgewertet.

Selbstverständlich werden die Daten anonym behandelt.

### Sehr wichtig:

1. Bitte lesen Sie die Packungsbeilage des Medikamentes erst nach dem ersten Teil des Fragebogens.
2. Wenn Sie mehrere Medikamente verschrieben bekommen haben, dann wählen Sie die Packungsbeilage desjenigen, mit dem Sie am wenigsten Erfahrung haben.
3. Falls Sie Antibiotika bekommen haben, dann wählen Sie bitte die Packungsbeilage dieses Medikamentes aus.
4. Wenn Sie den Fragebogen zurückgeben, bitte legen Sie auch Ihre Packungsbeilage bei.
5. Bitte bringen Sie den Fragebogen sobald wie möglich in die Arztpraxis oder Apotheke zurück, in der Sie ihn bekommen haben.

Das Projekt wird unter der Anleitung von Frau Prof. Elisabeth Gülich und Prof. Hans Strohner, Fakultät für Linguistik und Literaturwissenschaft, durchgeführt.

Wenn Sie Fragen dazu haben, wenden Sie sich bitte an:

Barbara Osimani  
Universität Bielefeld  
Fakultät für Linguistik und Literaturwissenschaft

<b>FRAGEBOGEN</b>
-------------------

Dieser Fragebogen besteht aus zwei Teilen. In dem ersten Teil wird an Hand Ihrer Angaben Ihr Informationsbedürfnis bewertet.

Erst nach dem ersten Teil werden Sie gebeten, die Packungsbeilage zu lesen.

Bitte machen Sie zu jeder Frage Angaben (Bei einigen Fragen und Aussagen sind auch Mehrfachangaben möglich).

**Erster Teil**

In den ersten Aussagen geht es hauptsächlich um Ihre Erfahrung mit dem Medikament, mit dem Sie behandelt werden.

1) **Name des Medikamentes:** \_\_\_\_\_

2) **Anwendungsbereich des Medikamentes:**

a) Ernährungsorgane (Bauch, Magen, Darm, Verdauungsstörungen, etc.)	[ ] <sub>a</sub>
b) Kreislauf	[ ] <sub>b</sub>
c) Haut	[ ] <sub>c</sub>
d) Atemwege (Husten, Halsschmerzen, etc.)	[ ] <sub>d</sub>
e) Knochen/Muskel (Muskelkater, Gelenkentzündungen, etc.)	[ ] <sub>e</sub>
f) Sonstiges:	[ ] <sub>f</sub>

3) **Typ des Medikamentes:**

a) Antibiotika	[ ] <sub>a</sub>
b) Schmerzmittel	[ ] <sub>b</sub>
c) Blutdruckmedikamente	[ ] <sub>c</sub>
d) Antidiabetika	[ ] <sub>d</sub>
e) Sonstiges:	[ ] <sub>e</sub>

4) **Krankheit:** \_\_\_\_\_

5) **Seit wann leiden Sie unter dieser Krankheit? Seit** \_\_\_\_\_

<b>6) Nehmen Sie dieses Medikament jetzt zum ersten Mal?</b>	a) Ja.....	[ ] <sub>a</sub>
	b) Nein.....	[ ] <sub>b</sub>
<b>7) Haben Sie auch andere Medikamente für die Behandlung derselben Krankheit benutzt?</b>	a) Ja.....	[ ] <sub>a</sub>
	b) Nein.....	[ ] <sub>b</sub>
(machen Sie bitte mit der Frage 9 weiter)		
<b>8) Warum haben Sie das Medikament gewechselt? (Mehrangaben möglich)</b>		
a) Das andere Medikament wurde vom Markt genommen.....		[ ] <sub>a</sub>

b) Das andere Medikament hatte eine geringere Wirkung.....	[ ] <sub>b</sub>
c) Das andere Medikament konnte ich nicht gut vertragen.....	[ ] <sub>c</sub>
d) Der Arzt hat eine Alternative zum alten gefunden .....	[ ] <sub>d</sub>
e) Sonstiges.....	[ ] <sub>e</sub>

<b>9) Was wäre die Konsequenz einer Nicht-Behandlung?</b>	
a) Ich müsste ein paar Tage zu Hause bleiben .....	[ ] <sub>a</sub>
b) Es könnte eine Verschlechterung geben, die noch schwerer zu behandeln wäre.....	[ ] <sub>b</sub>
c) Ich müsste mich operieren lassen .....	[ ] <sub>c</sub>
d) Ich weiß es nicht .....	[ ] <sub>d</sub>
e) Sonstiges: _____	[ ] <sub>e</sub>
_____	
_____	

**Zum Beispiel**

Im Folgenden werden Sie gebeten, Ihre Angaben in einer Skala von 0 bis 100 numerisch anzugeben. Die Zahl sollte an der entsprechenden Stelle in der Linie eingefügt werden. So z.B., bei der folgenden Frage:

<b>Ich mache gerne Urlaub in der Schweiz.</b>	
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wenn Sie gerne in der Schweiz Urlaub machen, aber nicht gerade sehr gerne, können Sie z.B. einen Wert von 75 angeben. Dann tragen Sie bitte an dieser Stelle ein X in die Skala ein und schreiben den entsprechenden Wert darunter:

<b>Ich mache gerne Urlaub in der Schweiz.</b>	
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**Bitte geben Sie Ihre Angaben bei den folgenden Fragen nach dem eben erklärten Schema ein:**

<b>10) Sind Sie mit der Wahl des Medikamentes zufrieden?</b>	
<b>11) Wie viele Informationen haben Sie über das Medikament?</b>	

	ich nicht	
<b>12) Gibt es noch etwas, das Sie unsicher macht? (Bitte ankreuzen)</b>	a) Ja.....	<input type="checkbox"/> a
	b) Nein (machen Sie bitte mit der Frage 15 weiter)....	<input type="checkbox"/> b

**13) Was ist das?**

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<b>14) Könnte eine eventuelle Aufklärung darüber die Unsicherheit abschaffen?</b>	
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<b>15) Erwägen Sie, auf Grund eventuell mangelnder Information das Medikament nicht einzunehmen?</b>	
--	--

<b>16) Für wie verlässlich halten Sie die folgenden Informationsquellen?</b>	
<b>a) Arzt</b>	
<b>b) Apotheker</b>	
<b>c) Freunde/ Angehörige</b>	
<b>d) Meine eigene Erfahrung</b>	
<b>e) Packungsbeilage</b>	
<b>f) Fernseh- /Radiosendungen</b>	
<b>g) Artikel in der Presse</b>	
<b>h) Information im Internet</b>	
<b>i) Werbung</b>	
<b>h) Sonstiges:</b> _____ _____ _____	

<b>17) Wie wurde das Medikament gewählt? (Mehrfachangaben möglich)</b>	
a) Der Arzt hat es mir verschrieben.....	<input type="checkbox"/> a

b) Der Arzt hat es mir empfohlen und ich habe den Vorschlag angenommen .....	[ ] <sub>b</sub>
c) Nach gemeinsamer Überlegung mit dem Arzt, hat sich herausgestellt, dass dieses Medikament auf mich am besten wirken kann.....	[ ] <sub>c</sub>
d) Nach gemeinsamer Überlegung mit dem Arzt, hat sich herausgestellt, dass ich mit diesem Medikament am wenigsten Nebenwirkungen haben werde. ....	[ ] <sub>d</sub>
e) Es gibt keine Alternative. ....	[ ] <sub>e</sub>
f) Ich weiß von keiner Alternative.....	[ ] <sub>f</sub>
g) Sonstiges: _____	[ ] <sub>g</sub>

<b>18) Wie viel Erfahrung haben Sie bereits mit Medikamenten?</b>	
<b>19) Bei Ihnen wirken Medikamente:</b>	

Ihre Erfahrung mit Nebenwirkungen:

<b>20) Wenn ich krank bin, dann ist es schwer für mich zwischen Symptomen der Krankheit und Nebenwirkungen des Medikaments zu unterscheiden.</b>	
<b>21) Man muss Nebenwirkungen in Kauf nehmen, wenn man ein Medikament einnimmt.</b>	

### Zum Beispiel

Bei den folgenden Fragen können Sie entweder die linke (a) oder die rechte (b) Antwort geben. So zum Beispiel bei der folgenden Aussage können Sie Antwort a) ankreuzen falls Sie keine Idee davon haben, wie teuer ein Urlaub in der Schweiz ist:

<b>Urlaub in der Schweiz ist teuer.</b>	
a) Ich kann es nicht beurteilen	

Falls Sie b) wählen, dann sollte die Antwort in einer Schätzung nach dem bekannten Schema bestehen.

Hier kann aber die Einschätzung in zwei Varianten angegeben werden: Entweder nach dem bekannten Schema:

<b>Urlaub in der Schweiz ist teuer.</b>	
a) Ich kann es nicht beurteilen	

Oder in der folgenden Weise: Falls Sie nicht eine genaue Nummer angeben können, aber ihre Schätzung zwischen zwei Nummern liegt (z.B. zwischen 60 und 90) dann kennzeichnen Sie diesen Bereich mit einem Kreis:

<b>Urlaub in der Schweiz ist teuer.</b>	
a) Ich kann es nicht beurteilen	b)

<b>22) Ich habe in der Vergangenheit Nebenwirkungen gehabt, wenn ich ein Medikament genommen habe.</b>	
a) Ich kann es nicht beurteilen (Machen Sie bitte mit der Frage 24 weiter).	b)

**23) Von diesen waren ungefähr \_\_\_\_\_ % schwere und \_\_\_\_\_ % leichte Nebenwirkungen (Bitte Prozent angeben).**

<b>24) Wie effektiv finden Sie das vorliegende Medikament im Verhältnis zu alternativen Behandlungen zur selben Krankheit?</b>	
a) Ich kann es nicht beurteilen	b)

<b>25) Wie optimal werden Sie auf die Behandlung reagieren?</b>	
a) Ich kann es nicht beurteilen	b) Meiner Meinung nach werde ich:
auf die Behandlung reagieren.	

<b>26) Glauben Sie, dass das vorliegende Medikament im Verhältnis zu alternativen Behandlungen zur selben Krankheit <i>schwere</i> Nebenwirkungen hat?</b>	
a) Ich kann es nicht beurteilen	b)

<b>27) Glauben Sie, dass das vorliegende Medikament im Verhältnis zu Alternativen Behandlungen zur selben Krankheit <i>viele</i> Nebenwirkungen hat?</b>	
a) Ich kann es nicht beurteilen	b)

<b>28) Wie wahrscheinlich ist es, dass Sie von den Nebenwirkungen dieses Medikamentes betroffen werden?</b>	
a) Ich kann es nicht beurteilen (Machen Sie bitte mit der Frage 30 weiter).	b) 

29) Von diesen werden \_\_\_\_\_% schwere und \_\_\_\_\_% leichte Nebenwirkungen sein.

<b>30) Finden Sie dass die positiven Wirkungen dieses Medikamentes die eventuellen Nebenwirkungen übersteigen? (Auf Sie bezogen)</b>	a) Ja.....	[ ] <sub>a</sub>
	b) Nein .....	[ ] <sub>b</sub>
	c) Ich kann es nicht beurteilen.....	[ ] <sub>c</sub>
	(machen Sie bitte mit der Frage 32 weiter)	

31) Bei der folgenden Summe sollen Sie Ihre Einschätzung über die Gesamtwirkung des Medikamentes angeben. Tragen Sie bitte die Zahlen ein, die ihrer Meinung nach die Aufteilung in positiver Wirkung und Nebenwirkungen am besten darstellen:

Positive Wirkungen	Nebenwirkungen			
		+	=	100

32) Lesen Sie jetzt bitte aufmerksam die Packungsbeilage des Medikamentes. Bitte heben Sie die Stellen des Textes hervor, die Sie wichtig finden und schreiben Sie hierunter warum: z.B. weil sie unverständlich, mehrdeutig oder unklar sind, oder auch weil es sich um Informationen handelt, wovon Sie vorher nicht wussten, etc.

Bitte markieren Sie die entsprechende Nummer auf dem Beipackzettel.

- 1).....  
.....  
.....
- 2).....  
.....  
.....
- 3).....  
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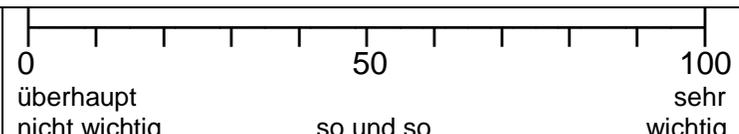
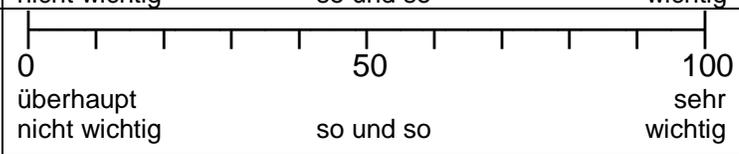
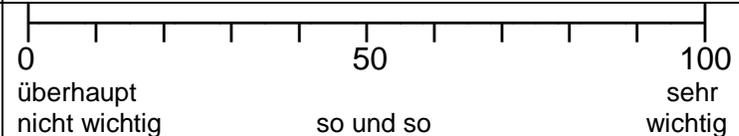
4).....  
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5).....  
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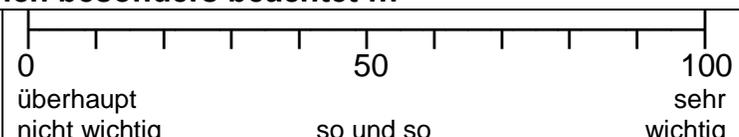
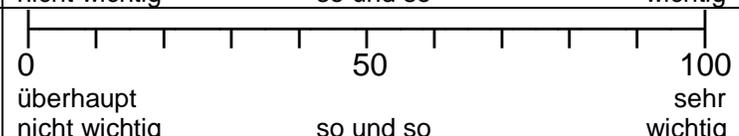
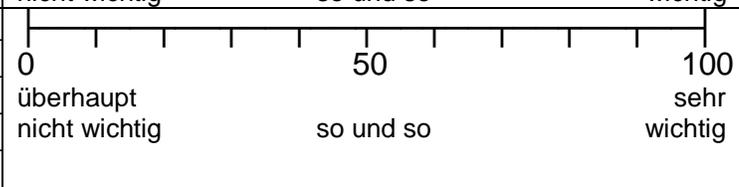
6).....  
 .....  
 .....

7).....  
 .....

**Nun einige Fragen über Ihr Leseerlebnis:  
 Beim Lesen der Packungsbeilage war es wichtig ...**

<b>33) ... die Information mit meiner Erfahrung über Medikamente zu vergleichen.</b>	
<b>34) ... die Information mit anderen Informationen aus anderen Quellen (Medien, Arzt, Freunde, etc.) zu verbinden.</b>	
<b>35) ... mir vorzustellen, wie das Arzneimittel funktioniert.</b>	

**Beim Lesen der Packungsbeilage habe ich besonders beachtet ...**

<b>36) ... die Informationen, die ich im Widerspruch zu meinen Kenntnissen fand.</b>	
<b>37) ... die Informationen, die in der Packungsbeilage widersprüchlich zueinander waren.</b>	
<b>38) Sonstiges:</b> _____ _____ _____ _____	

**39) Ich finde die Information dieser Packungsbeilage:**

a) ausreichend	0 50 100 überhaupt nicht so und so absolut ja
b) schon bekannt	0 50 100
c) überflüssig	0 50 100
d) beängstigend	0 50 100
e) nützlich	0 50 100
f) sonstiges: _____ _____ _____	0 50 100

### Zweiter Teil

Nun werden einige der obigen Fragen wiederholt. Es geht darum zu wissen, was für Informationen Sie von der Packungsbeilage erhalten haben.

40) Sind Sie mit der Wahl des Medikaments zufrieden?	0 50 100 überhaupt nicht so und so völlig zufrieden
--	--

41) Ich bin unsicher, ob ich die Behandlung mit dem Medikament überhaupt anfangen.	0 50 100 nicht anfangen ich weiß nicht anfangen
--	--

42) Ich werde das Medikament zunächst einmal einnehmen.	0 50 100 nicht einnehmen ich weiß nicht einnehmen
---	--

43) Ich möchte noch einmal mit dem Arzt über das Medikament sprechen	0 50 100 Nein, überhaupt nicht ich weiß nicht definitiv ja
--	---

44) Wie viele Informationen haben Sie jetzt über das Medikament?	0 50 100 überhaupt keine einige mehr brauche ich nicht
--	---

45) Gibt es noch etwas, das Sie unsicher macht?	a) Ja..... b) Nein (machen Sie bitte mit der Frage 48 weiter)	[ ] [ ] a b
---	--	----------------------

46) Was ist das? \_\_\_\_\_  
\_\_\_\_\_

<b>47) Könnte eine eventuelle weitere Aufklärung die Unsicherheit abschaffen?</b>	
---	--

<b>48) Erwägen Sie, auf Grund eventuell mangelnder Information das Medikament nicht einzunehmen?</b>	
--	--

<b>49) Würden Sie sich vor Fortsetzung der Therapie nach weiteren Informationen suchen?</b>	
---	--

An Hand der Information, die Sie von der Packungsbeilage bekommen haben:  
(Beantworten Sie nach dem Schema der Fragen 22-28)

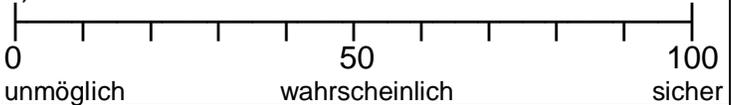
<b>50) Wie effektiv finden Sie das vorliegende Medikament im Verhältnis zu alternativen Behandlungen zur selben Krankheit?</b>			
a) Ich kann es nicht beurteilen	<table border="1"> <tr> <td style="width: 40%;"><b>b)</b></td> <td> </td> </tr> </table>	<b>b)</b>	
<b>b)</b>			

<b>51) Wie optimal werden Sie auf die Behandlung reagieren?</b>			
a) Ich kann es nicht beurteilen	<table border="1"> <tr> <td style="width: 40%;"><b>b) Meiner Meinung nach werde ich:</b></td> <td> </td> </tr> </table>	<b>b) Meiner Meinung nach werde ich:</b>	
<b>b) Meiner Meinung nach werde ich:</b>			

<b>52) Glauben Sie, dass das vorliegende Medikament im Verhältnis zu alternativen Behandlungen zur selben Krankheit <i>schwere</i> Nebenwirkungen hat?</b>	
a) Ich kann es nicht beurteilen	

<b>53) Glauben Sie, dass das vorliegende Medikament im Verhältnis zu alternativen Behandlungen zur selben Krankheit <i>viele</i> Nebenwirkungen hat?</b>	
a) Ich kann es nicht beurteilen	

<b>54) Wie wahrscheinlich ist es, dass Sie von den Nebenwirkungen dieses Medikaments betroffen werden?</b>	
--	--

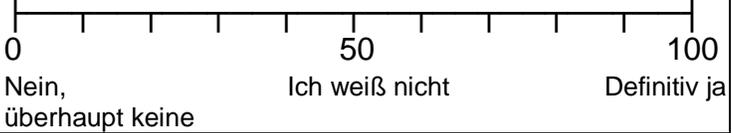
a) Ich kann es nicht beurteilen (Machen Sie bitte mit der Frage 57 weiter).	b) 
--	---

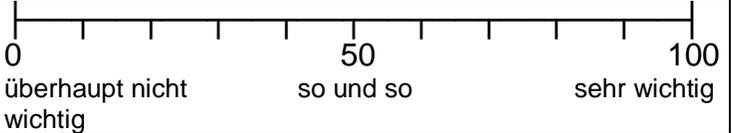
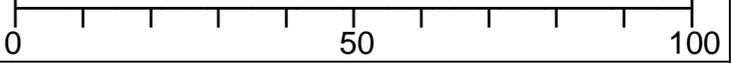
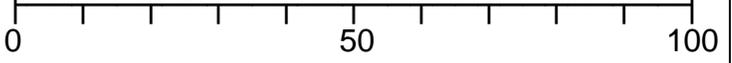
55) Von diesen werden \_\_\_% schwere und \_\_\_% leichte Nebenwirkungen sein.

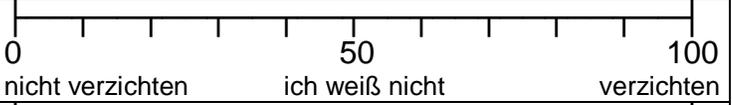
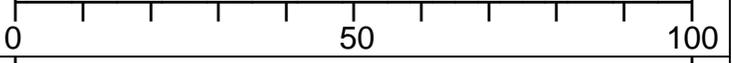
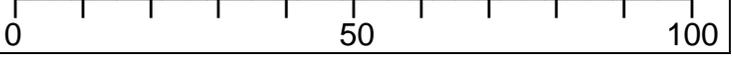
56) Finden Sie dass die Wirkungen dieses Medikamentes die eventuelle Nebenwirkungen übersteigen? (Auf Sie bezogen)	a) Ja..... b) Nein ..... c) Ich kann es nicht beurteilen (machen Sie bitte mit der Frage 58 weiter)	[ ] <sub>a</sub> [ ] <sub>b</sub> [ ] <sub>c</sub>
---	--	--

57) Bei der folgenden Summe sollen Sie Ihre Einschätzung über die Gesamtwirkung des Medikamentes angeben. Tragen Sie bitte die Zahlen ein, die ihrer Meinung nach die Aufteilung in positiver Wirkung und Nebenwirkungen am besten darstellen:

Positive Wirkung	+	Nebenwirkungen	=	100

58) Würden Sie noch weitere Informationen in der Packungsbeilage hinzufügen lassen?	
---	--

59) Welche Wichtigkeit würden diese weiteren Informationen haben?	
a) Wie das Arzneimittel wirkt in meinem Körper	
b) Erfolgswahrscheinlichkeit der Therapie	
c) Sonstiges: _____ _____	

60) Würden Sie auf folgende Teile der Packungsbeilage verzichten?	
a) Zusammensetzung	
b) Anwendung	
c) Warnungen	

d) Dauer und Dosis	
e) Sonstiges: _____ _____	

61) Warum würden Sie darauf verzichten? \_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

Nun ein paar Fragen über Ihre Lesegewohnheiten mit Packungsbeilagen.

62) Ich lese die Packungsbeilage:	
-----------------------------------	--

Ich lese die Packungsbeilage ...

63) ...bevor ich mit der Behandlung überhaupt anfangen:	
64) ... erst dann, wenn bei der Behandlung unerwartete Wirkungen entstehen:	
65) Ich lese den ganzen Text.	

66) In der Packungsbeilage lese ich hauptsächlich: \_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

67) Was für eine Funktion/Funktionen haben Packungsbeilage Ihrer Meinung nach?

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

Abschließend bitte ich Sie, einige allgemeine Informationen zu Ihrer Person und zu Ihrem Gesundheitszustand anzugeben:

68) Alter: \_\_\_\_\_

69) Geschlecht:  
 a) weiblich ..... [ ]<sub>a</sub>  
 b) männlich ..... [ ]<sub>b</sub>

<b>70) Bildungsstand:</b>	
a) Hauptschulabschluss	[ ] <sub>a</sub>
b) Realschulabschluss	[ ] <sub>b</sub>
c) Abitur	[ ] <sub>c</sub>
d) Universitäts-/ Fachhochschulabschluss	[ ] <sub>d</sub>
e) Sonstige	[ ] <sub>e</sub>
f) Medizinstudent (oder Fächer der Gesundheitswiss.)	[ ] <sub>f</sub>

<b>71) Beruf:</b>	
a) Arbeiter/in	[ ] <sub>a</sub>
b) Angestellter/in	[ ] <sub>b</sub>
c) Beamter/in	[ ] <sub>c</sub>
d) Selbständig	[ ] <sub>d</sub>
e) Hausfrau/mann	[ ] <sub>e</sub>
f) Student/in-Azubi	[ ] <sub>f</sub>
g) Arbeitslos	[ ] <sub>g</sub>
h) Gesundheitsberuf (Arzt/ Krankenpfleger...)	[ ] <sub>h</sub>
i) Sonstige	[ ] <sub>i</sub>

72) Gesundheitszustand (Mehrfachangaben möglich):

Ich leide an:

a) einer
b) mehreren

c) leichten
d) schweren
e) chronischen

Beschwerde(n)
---------------

73) Ich bin insgesamt:	0	50	100
	schwer krank		kerngesund

74) Ich nehme zur Zeit andere Medikamente	a) Nein.....	[ ] <sub>a</sub>
	b) Ja .....Wie viele?.....	[ ] <sub>b</sub>

75) Ich finde diesen Fragebogen:	
a) interessant	0   50   100 überhaupt nicht   so und so   absolut ja
b) schwer	0   50   100
c) lang	0   50   100
d) beängstigend	0   50   100
e) nützlich	0   50   100
f) sonstiges: _____	0   50   100

	0	50	100
--	---	----	-----

Wir bedanken uns sehr für Ihre Mitarbeit und freuen uns sehr darauf, Ihren Fragebogen entgegenzunehmen.

**Vergessen Sie nicht, die Packungsbeilage, die Sie dabei benutzt haben, dem Fragebogen beizulegen.**

Wenn Sie noch Fragen zu dieser Studie haben oder weitere Anmerkungen zum Fragebogen haben, dann wenden Sie sich an:

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Handy: 0162 – 1585563

**Falls Sie auch an der zweiten Phase der Studie teilnehmen wollen, können Sie hierunter Ihre Rückrufnummer (oder Ihre E-Mail-Adresse) hinterlassen:**

**Vielen Dank!**



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