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MEDIC Metodologia Didattica e Innovazione Clinica – *Nuova Serie*
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La rivista MEDIC *New Series*, Metodologia Didattica ed Innovazione Clinica si caratterizza per un approccio globale e unitario ai temi della Salute e della Formazione Bio-Medica. Essa intende proporsi come uno spazio di dialogo tra le cosiddette *due culture*, quella scientifica e quella umanistica, nello sforzo di offrire spunti di riflessione e di confronto alla luce di un neo-umanesimo medico che ha nella persona il suo punto di coesione e di equilibrio. Si tratta di una rivista scientifica multidisciplinare, che ospita revisioni della letteratura e lavori originali, nonché editoriali, lettere all'editore su argomenti di particolare interesse e recensioni di libri.

La rivista si propone di fornire un'occasione di confronto sul piano internazionale attraverso la pubblicazione di contributi attinenti alle seguenti sezioni: *Metodologia*, *Epidemiologia*, *Clinica e Ricerca di Base*, *Educazione Medica*, *Filosofia della Scienza, Sociologia della Salute* ed *Economia Sanitaria*, *Ingegneria Bio-Medica*, *Etica ed Antropologia*, *Storia della Medicina*.

Uno degli obiettivi prioritari della rivista è aprire un dibattito sui temi di maggiore rilievo scientifico in ambito bio-medico, affrontandoli sotto diverse angolature attraverso i contributi dei vari autori. MEDIC *New Series* vuole in tal modo offrire agli studiosi che si confrontano con le grandi questioni della salute e della malattia, della vita e della morte, del dolore e della sofferenza, uno scambio fecondo con colleghi di altre discipline**,** perché si giunga a una composizione del tema più ampia di quella consentita dall'esclusiva ottica della propria specialità.

Il dialogo tra le Scienze, per essere efficace e fruttuoso, deve essere prima di tutto un dialogo tra scienziati, capaci di analizzare la realtà anche con linguaggi diversi, per comprenderne aspetti che altrimenti resterebbero sottintesi o non sufficientemente elaborati e strutturati.

Ciascun manoscritto sottoposto per la pubblicazione verrà selezionato dai membri del Comitato Editoriale, in base alla tipologia di manoscritto e all'argomento contenuto, e sarà inviato dal responsabile della sezione specifica a due *referee* esperti che formuleranno un giudizio motivato. La decisione finale sull'accettazione del manoscritto verrà presa dal Comitato Editoriale, dopo aver conosciuto i pareri dei *referee*.

The scientific journal MEDIC New Series, Methodology & Education for Clinical Innovation distinguishes itself for its global and harmonious approach to Healthcare and Biomedical education issues. It wishes to foster the dialogue between the so called two cultures, the scientific and the humanistic one, in its effort to offer occasions of reflection and of confrontation in the light of a medical neohumanism which sees in the human being its point of cohesion and balance. It is a multidisciplinary scientific journal publishing literature reviews, original papers, editorials, letters to the Editor on topics of special interest as well as book reviews.

The journal intends to set up a space of comparison at an international level through the publication of papers relevant to the following sections: Methodology, Epidemiology, Clinical Medicine and Basic Research, Medical Education, Philosophy of Science, Health Sociology and Health Economics, Biomedical Engineering, Ethics and Anthropology, Medical History.

The journal's most important objectives is that of opening a debate on subject-matters of great scientific importance in biomedicine, tackling them from different view points through the contribution of various authors. Thus MEDIC New Series wishes to offer to scholars dealing with important issues such as health and sickness, life and death, pain and suffering, the opportunity of having a debate with colleagues of other disciplines so to make such discussion wider than it would be possible from the view point of a single specialty.

To make the dialogue among Sciences effective and fruitful, first of all it has to be a dialogue among scientists capable of analysing reality by using different languages, so to understand aspects that otherwise would be left unsaid or not sufficiently studied and explained.

Each manuscript submitted to publication will be selected by the members of the Editorial Board, on the basis of its typology and on its topic. It will be then sent by the responsible of the specific section to two expert referees who will express a motivated judgement. The final decision on the manuscript acceptance will be taken by the Editorial Board after having read the referees' opinion.

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The Epistemic Nature of Package Leaflet Information: a Contribution to the Legal Debate on the Role of Package Leaflets in Therapeutic Consent

La Natura Epistemologica dei Foglietti Illustrativi: un Contributo al Dibattito Legale sul loro Ruolo Relativamente al Consenso Informato

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Background 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. This article presents the results of a doctoral dissertation devoted to the legal and communicative analysis of PL information.
After illustrating the articulation of pharmaceutical risk through risk prevention norms (residual risk, development risk), the paper 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.

Index Terms Package leaflets information, Informed consent

Premessa *I foglietti illustrativi fanno parte del complesso sistema comunicativo volto alla minimizzazione e prevenzione del rischio farmaceutico. La loro natura legale tuttavia, non si esaurisce all'ambito della precauzione: quale forma privilegiata di istruzioni allegate al prodotto, sono oggetto di normativa del danno civile con relativa distribuzione della responsabilità sul rischio residuo (Kojuncu, 2006).*
Il presente contributo riassume i dati principali di una tesi dottorale dedicata all'analisi legale e comunicativa dei foglietti illustrativi. La prima parte illustra la ricca articolazione giuridica in ambito di prevenzione del rischio. Proprio riguardo alla distinzione tra rischio evitabile e inevitabile (residuo) vengono a distinguersi due funzioni comunicative fondamentali del foglietto illustrativo in analogia e a complemento dell'informazione fornita dal medico durante la consultazione: l'istruzione vera e propria volta a prevenire il rischio evitabile; e la dichiarazione del rischio inevitabile quale base per la libera decisione dell'utente (consenso informato).
La seconda parte analizza il contesto decisionale in cui il consumatore si trova coinvolto nell'acquisire informazioni dal foglietto illustrativo e valuta tale supporto informativo quale base per il consenso informato sulla base di categorie tipiche della teoria della decisione.
Infine una parte empirica indaga l'impatto del foglietto illustrativo nella decisione terapeutica e ne esamina il valore percepito su un campione di 55 consumatori.

Parole Indice *Foglietti illustrativi,Consenso Informato*

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Introduction: pharmaceutical information towards the patient

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.[1]

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 and the requirement of safety.[2]

Debates about pharmaceutical products focus on one and the same concern: Health as an individual and societal good, which drugs contribute to promote and to endanger 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 self-determination and freedom of choice with respect to the risks associated with pharmaceutical products. In this sense, information should warrant decision autonomy both to the prescribing physician and to the patient.[3]

The importance of product instruction for therapeutic safety is especially linked to the use of pharmaceutical products in home therapy, where patients cannot be monitored and supported as accurately as in the inpatient setting.

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.[4]

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[1] For a recent discussion see: Gaßner, Reich-Malter, 2006: 147 ff.

[2] 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 (1st amendment), 1986 (2nd), 1988 (3rd), 1990 (4th and 5th), 1996 (6th), 1998 (7th and 8th), 1999 (9th), 2000 (10th), 2002 (11th), 2004 (14th), 2005 (13th, 14th, 15th).
A detailed historical account of the juridical path leading to the actual state of the art with special reference to the German legislation can be found in Scheu, 2003.

[3] In both cases the decision is based upon the evaluation of the alternative options and their consequences as they can be gauged by the available information. Information becomes therefore the necessary condition for the decision-maker to perform an autonomous evaluation of the options available and to choose one of them in accordance to his preferences and values. Because of the endemic incompetence in dealing with medical matters, the concept of autonomous decision for lay decision makers in the medical setting is however difficult to circumscribe and raises complex ethical and philosophical problems. The concluding part of this article presents some questions pertaining to the definition of this concept, which the legal/philosophical analysis of the institute of informed consent should take into account.

[4] In particular, the European directive 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 annexed 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 14th 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 14th 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."

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.[5] 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)[6] has emphasized the patient's responsibility in taking notice of the risks reported in the package leaflet as a basis for his own risk/benefit evaluation and therapeutic decision.

– In contrast to this sentence, other decisions,[7] 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.[8]

In fact, differently than in the U.S., where no legal value is assigned to pharmaceutical product instruction, and the theory of "learned intermediary"[9] imposes information duties only on the doctor, PL information has in Germany a specific binding force for the drug consumer, which is nevertheless difficult to define precisely because of the information duties also imposed on the doctor.

This article illustrates the main conclusions presented by a doctoral dissertation[10] devoted to the examination and evaluation of package leaflets 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. Legal analysis of PL information

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.

Safety information should prevent avoidable risk to occur; instead self-determination information should declare the unavoidable residual risk, so as to insure that the drug user is aware of it when he decides whether to undertake the therapy or not.

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.

Residual risk in general is the risk which cannot be excluded with absolute safety, but which can be regarded as improbable (and/or insignificant) enough to be considered legally irrelevant. In the case of drug prescription, residual risk is the foreseeable damage which can be considered to be compensated by the risks connected to the illness.

The threshold is established in two stages: (i) in the drug approval procedure and (ii) in the risk/benefit assessment made by the doctor.

(i) Given the impossibility of absolute safety for pharmaceuticals, the evaluation of drugs cannot result in a distinction between harmfulness and innocuousness but rather between an acceptable ("zumutbar") and an unacceptable ("unzumutbar") risk.[11] This is a relational judgment and is done by relating the drug risks to its expected benefit and

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[5] 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 – 15.3.2006 – the BfArM (Bundesinstitut für Arzneimittel und Medizinprodukte – the German Federal Office for Drugs and Medical Devices – has organized a seminar for investigating the state of the art as for PLs readability and patient friendliness. http://www.bfarm.de/cln_042/nn_599148/-DE/BfArM/Publikationen/Praesentationen/060215-Dialog.html Bonn, 15.3.2006.

[6] LG Dortmund, MedR 2000, 332.

[7] BGH, 14. 3. 2006 (NJW 2006: 2108); BGH 15. 3. 2005, NJW 2005, 1716 (1718); BGH 15. 2. 2000 (NJW 2000, 1784).

[8] See Koyuncu, 2006, 2005a, 2005b, 2005c, 2005d; Müller, 2006, Fries, 2006; Bergmann, 2005, Blasius, 2005; Oehlschläger, 2005; Hart, 2003; Schlund, 1999.

[9] See for a detailed discussion Fergusin, 1992.

[10] Osimani, 2007. The dissertation has been made possible through a doctoral grant from the Swiss National Fund for research.

[11] Drug approval and access to the market is regulated by 5 AMG. See also Räpple, 1991: 50-57.

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 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.[12] The tolerance threshold refers to this comparison and determines the line above which a drug is declared as "bedenklich" (unsafe).[13]

(ii) With the general safety judgment ("Unbedenklichkeit") about a pharmaceutical *product*, it is yet said nothing about its safe *use*.[14] 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. A drug which has a *general positive risk/benefit evaluation* can show a *negative risk/benefit profile for a specific user*. 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.[15]

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.[16] 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.[17] Figure 1 shows the "residual risk areas" for the pharmaceutical product and for the therapeutic prescription.

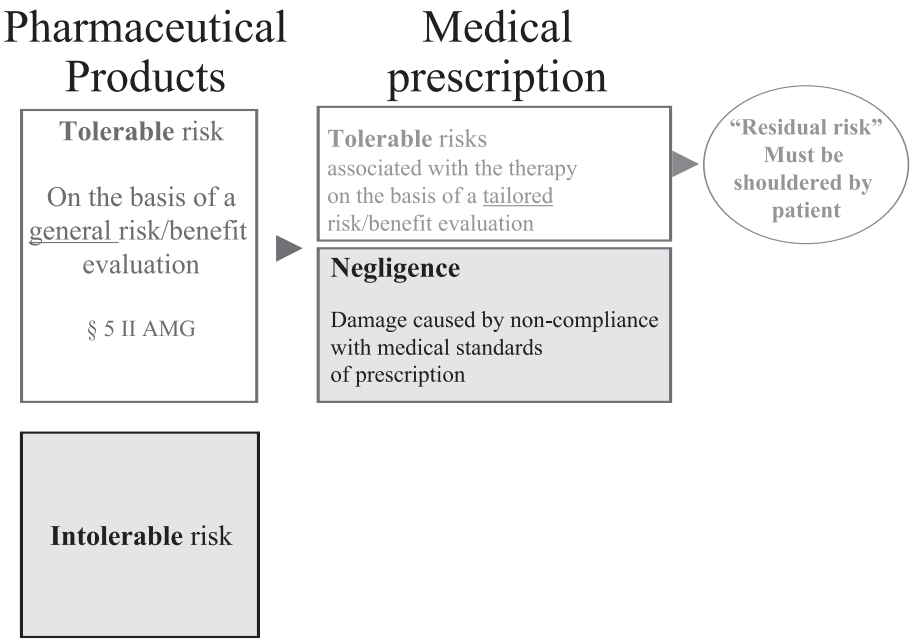

Figure 1. Residual risk for the pharmaceutical product and for the therapeutic prescription.

[12] Räpple, 1991: 110. Scheu, 2003: 713.
[13] See Krudop-Scholz: 2005: 145.
[14] Krudop-Scholz, 2005: 147.
[15] Hart, 2003, 603. Francke, Hart, 1999: 60.
[16] See Hart, 2003: 605.
[17] 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.

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.

Consequently, any risk falling within the tolerance line is considered acceptable (or tolerable) and it is considered "residual risk".

Because disclosure of residual risk is also performed by the doctor, two steps are needed in order to evaluate the legal/communicative role of PLs in this framework:

1. the analysis of risk disclosure within the institute of informed consent (chapter 3);
2. the analysis of the responsibility spheres regarding the information of residual risk (chapter 4);

Within point 1 two issues have been touched:

1.1 The repercussions of the 2nd Amendment Law for Compensation on doctor-patient communication;

1.2 The communicative status of therapeutic information under the tort and the contract liability regimes respectively.

1.1 Doctor-Patient Communication after the 2nd Amendment Law for Compensation

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 individual liberties and autonomy brought about by a new right-orientation (civil rights and consumer rights).[18] 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 his bodily integrity and health.[19]

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",[20] and 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".[21]

In order for consent to be valid however, it must be given in observance of the right to autonomy and self-determination[22], 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, and thereby equates to a risk disclaimer.

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*.

This debate has only recently found a solution with the disentanglement of indemnity for information failures from 823.1 BGB through the 2nd Amendment Law for Damage compensation.[23] In fact, through the amendment of § 253 Abs. 2 BGB and the abolishment of § 847 BGB,

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[18] Faden, Beauchamp, 1986: 23-143.

[19] Reichsgericht 31.5.1894, Strafs. Bd. 25, nr. 127: 375: "Ein Arzt der vorsätzlich für Heilzwecke eine Körperverletzung verübe, ohne sein Recht heirzu aus einem bestehenden Vertragsverhältnisse oder einer präsumtiven Zustimmung, dem vermuteten Auftrage hierfür legitimierter Personen, herleiten zu können, handelt überhaupt unberechtigt, also rechtswidrig".

[20] 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 (see Wagner, 2004:1473) and then extends the obligation to compensate only indirectly to other goods in the second paragraph through reference to specific laws.

[21] "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.

[22] 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".

[23] II Schadensersatzänderungsgesetz, 2SchadÄndG: 25.7.2002 BGBl I S 2674.

the 2nd Amendment Law of Compensation extends compensation for moral damage (damage for pain and sufferings) – which were previously limited by § 847 BGB to torts – to breaches of contract.

The importance of this change for doctor-patient communication lies in the fact that by subsuming lack of adequate information under a contract violation, this need not be associated with material damage (health impairment, pecuniary losses).[24]

It has been observed that by allowing the claim for moral damage 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).[25]

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 damage. 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.[26]

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 damage 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 with 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.

1.2 Communicative status of therapeutic information under tort and contract liability

In the informed consent model entailed by the tort liability regime, doctor-patient communication serves the purpose of legitimizing the medical procedure. In the counselling 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 differs 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 counselling 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.

Following this analysis, 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.

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[24] Moral damage is generally identified with non-pecuniary losses such as psychological distress, loss of enjoyment of life and is measured through quality of life scales (see for instance Bovbjerg et al. 1989). In this setting moral damage consists in the lost chance of being enabled to choose among concretely available options because of lack of comprehensive information.

[25] „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". Giebel, 2001, citing the BT-Drucks. 14/7752: 15 (my emphasis).

[26] 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 legitimization 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 [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.

2. Responsibility spheres regarding the information of residual risk

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 does 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 it is included in PL information (See Fig. 2).

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. Normative evaluation of PL information

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 PL information as a valid basis for informed consent.

The legal and socio-psychological literature has advanced different objections to PL information as an adequate basis for informed consent. They are presented and commented in the following.

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.[27]

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 the patient's decision, then 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, then 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*".[28]

1.4. "Non-tailoredness" of PL information. A decision can be considered self-determined, only if made on the basis of personally relevant information.[29] 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.[30]

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[31] 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.[32]

The delivery of perfectly tailored information would require a pharmaco-genomics screening and is not feasible at the moment, therefore it cannot be demanded from a stan-

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[27] Koyuncu, 2006: 344; 2005a: 76; 2005b: 291 ff.

[28] 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".

[29] "Selbstbestimmt ist die Entscheidung dann, wenn die aus der Sicht des Patienten entscheidungsrelevanten Informationen zur Verfügung stehen": Hart, 2003: 605.

[30] See Hart, 2003: 605; Krudop-Scholz, 2005: 156. See also Stöhr, 2006: 148.

[31] There are PLs with more than 80 side-effects: Grandt et al., 2005: 511. See also Schlund, 1999 for a juridical perspective on this particular issue.

[32] See Krudop-Scholz, 2005: 159-162.

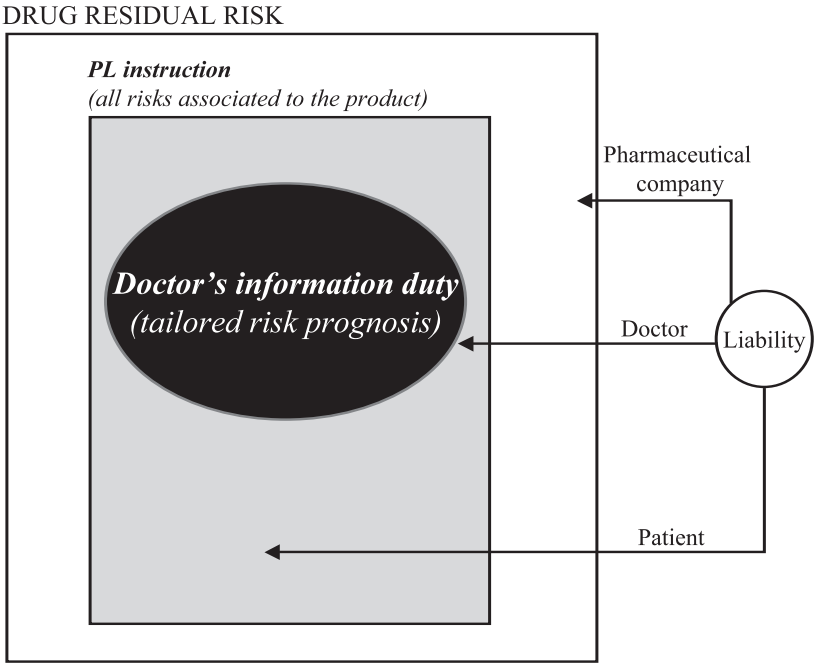

Figure 2. Liability distribution for residual risk among pharmaceutical firm (white), patient (grey), and doctor (black). By consenting to the therapy, the patient shoulders all the residual risk mentioned in the PL which does not belong to the realm of doctor's information duty.

dardized means of risk disclosure such as PL information.[33] Also adverse drug reactions which can be traced back to particular ethnic, morbidity, and environmental conditions[34] detected in observational studies and pharmacosurveillance cannot be always adequately addressed in the PL. The point at issue is however that precisely because of this inadequacy, PL information should not be legitimized as a source of responsibility offload for the pharmaceutical firm.

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.

The prima facie objections presented in this paragraph touch epistemological aspects of PL information as a basis for knowledge updating, risk/benefit assessment and therapeutic decision.

Therefore the evaluation of PL information must go beyond its linguistic and communicative aspects and investigate the role of PL information in the therapeutic decision. The methodological tool adopted for this analysis is Bayesian theory in that it has been developed for the analysis of the relationship between information and decisions under uncertainty, such as therapeutic decisions typically are.[35] 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*.[36]

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[33] I thank an anonymous referee for pointing out this issue and providing important and valuable suggestions on this and other relevant topics addressed in the article.

[34] See for instance: Goldstein et al., 2007; McDowell et al., 2006; Menezes de Pádua et al., 2005; Waller, Evans, 2003; Aronson, Ferner, 2003; Schwartz et al. 2001; Aronson, 2001; Henry et al., 1996; .Spielberg, 1993. Clericetti, Beretta-Piccoli, 1991; Hasselstrom et al., 1990; Dickinson et al., 1989; Mulhall et al., 1983; Greenblatt et al., 1981; Batchelor et al., 1980. For the implications related to the communication of risk probability in these settings see Calman, 1996.

[35] 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.

[36] "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).

2. Bayesian analysis of PL information

Bayesian theory comprehends three distinct but interconnected fields of research which are all relevant to the analysis of PL information:

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

These three fields jointly aim to describe the management of decisions under uncertainty. [37]

"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.

Decisions are modeled in Bayesian theory 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. 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:

	$\prod$	•	$\Leftarrow$
	S_1 .6	S_2 .3	S_3 .1
a_1 picnic	$Outcome_{11}$ **100**	$Outcome_{12}$ 0	$Outcome_{13}$ -100
a_2 big-town-sightseeing	$Outcome_{21}$ 0	$Outcome_{22}$ **70**	$Outcome_{23}$ - 20
a_3 museum	$Outcome_{31}$ - 100	$Outcome_{32}$ 0	$Outcome_{33}$ **80**

Figure 2. Decision matrix: columns represent relevant state of affairs with associated probabilities. The partition exhausts all possible events and events are mutually exhaustive (i.e. the sum of the individual probabilities equals 1). Rows represent alternative actions leading to different outcomes depending on the state of affair which comes to be true.

[37] Indeed, the emergence of decision theory is intrinsically intertwined with the evolution of subjective probability theory. Whereas first mathematicians and philosophers of science and than 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 modelled 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:

$SEU(a_1)$: $\sum P(S)U(a_1) = 100(.6) + 0(.3) + (-100)(.1) = 50$ ← max
$SEU(a_2)$: $\sum P(S)U(a_1) = 0(.6) + 70(.3) + (-20)(.1) = 19$
$SEU(a_3)$: $\sum P(S)U(a_1) = -100(.6) + 0(.3) + (80)(.1) = -52$

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.

Bayesian theory provide the framework 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.

The normative analysis of PL information is articulated into two points:

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

1. As for the first point, the requirements are derived from the right which the institute of informed consent should honour, 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.

2. In order to analyze whether PL information can be an adequate basis for consent to be valid, the PL role as a contributor to epistemic accuracy within the therapeutic choice has been evaluated on the benchmark of a model deriving from the decision constraints pertaining to the lay therapeutic decision.

The model is constituted by a two-components function (Andersson and Littkens, 2002). The first component is a traditional expected utility function (where utilities are weighted by probability assignments, as in the example above); the second is a generalized expected utility where health states (utilities) are surrounded by uncertainty and cannot be assigned firm probabilities:[38]

$$U(a) = \gamma(a) \cdot \sum_s \pi_s (a)\, u(h^s, a) + (1 - \gamma(a)) \cdot u_0(a).$$[39]

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, … 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:[40]

$$u_0(a) = \tilde{E}\, \{u\,(h, a) | \, \| \, S + 1, \ldots S + S'\}.$$

The weighting factor γ allows accounting for the effect of risk information which can simultaneously make people more genuinely uncertain (decrease of γ) and more pessimistic regarding the probability of a specific disease (higher probabilities are associated to less preferred states

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[38] 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 (π_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 γ reflects the degree to which the individual is confident about π_s and $\partial\pi_s/\partial a$ (though we cannot separate the two attitudes)".

[39] Andersson and Littkens (2002): 42. Andersson's and Littkens' analysis investigates the mathematical implications of this functions as for the effect of exogenous factors on the vector of activities a_1 (information gathering), a_2 (prevention), a_3 (consumption), and on their reciprocal influence. For the present purpose I consider a simplified interpretation of the function, where "a" stays for the act of taking the drug and the associated health implications: health state in terms of (quality adjusted) healthy days.

[40] 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, … 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: $u_0(a) = \sum v_s\, u(h^s, a)$.

in π_1 (a), … π_s (a)).[41] 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 favourable if it induces a shift in the distribution in the direction of stochastic dominance.[42]

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 favourable to the worst – being health states nothing else than 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 state) tends to 1 ($\gamma \rightarrow 1$).

Provided the principle of proportionality for risk disclosure, the amount of γ should be greater,

1. the greater the therapy risk is;
2. the less severe the illness is;
3. the less probable the benefit is.

Against the framework of this model, PL information reveals to decrease rather than increase the γ factor: i.e. to boost uncertainty. This is due both to the non-tailoredness of its probabilistic data for the individual prognosis, and to the lack of risk magnitude indexing.

There are in fact no legitimate epistemic grounds for directly assuming that the statistical frequency accompanying each side effect can be considered a reliable prognostic judgment about the probability that the 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. The doctor's task is precisely to combine both knowledge of the drug and of the patient in order to predict the risk level which the patient is exposed to by taking the drug.

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. This is a fundamental objection to the *legitimization of this instrument as a valuable basis for informed consent.* In fact, the legislator implies that consent is given with knowledge of the probabilities of risks and benefits.

PL information about side effects rather represents the hypotheses to be confirmed, than the answer to them: each side effect mentioned in the list generates uncertainty as to its possible occurrence, which the probabilistic data associated to it cannot substantially reduce: as a prognostic device, PL information fundamentally asks more questions than it answers.

Different considerations regard the safety function which PL information should also accomplish. 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.

III. Empirical findings

The normative analysis of PL information has been devoted to illustrate its specific *epistemic* nature and to demonstrate its insufficiency and redundancy at the same time.

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.[43]

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[41] "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 (γ) and in the probabilities (π)". Andersson and Littkens (2002): 43.

[42] 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.

[43] See also the list of *prima facie* objections presented above (especially points 1.5 and 1.6).

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.[44] 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*.[45]

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,[46] given the uncertainty sources identified at all discourse levels (lexical, semantic, and pragmatic) 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.[47]

However, a variety of responses to PL information or health risk information has been empirically observed.

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).[48]

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 reassuring information. 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. 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).

Laaksonnen, Duggan, Bates (2002) have found information seeking attitudes to be positively related to *past experience with side effects*. Moreover, high scorer 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.

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[44] BGH NJW 2000, 1784, 1787, f; BGH NJW 1985, 1399; BGH VersR 1973, 244 (246); VersR 1985, 361 (362).

[45] BGH 15. 3. 2005, NJW 2005, 1717

[46] Linguistic analyses of PL information 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; Hoffamnn, 1983; Saile 1984; Schuldt, 1992, 1998, Völzing, 1976, Zacharias, 1986).

[47] Bronder, Klimpel: 2001.

[48] 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).

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.[49] This is a considerable figure, but does not provide adequate ground for assuming that PL information invariably increase uncertainty.

In order to cast some light on this fragmentized scenery, empirical findings are presented at the end of the thesis. The last part of the work consists in fact 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. Survey

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

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

i. impact variance on benefit and risk assessments;
ii. absolute no impact on the decision.

PL reading has practically no average impact on the risk/benefit assessment. This is not only due to the lack of a systematic change direction (e.g. risk perception increase and decrease), but also 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). Little more than one third of the sample respondents (36.4%) have become more aware of the risks associated to the therapy after reading the PL. An equally consistent part of participants (30,3%) have delivered the same risk assessment before and after reading the PL. And, for another considerable portion of the participants (33,3) the perceived personal risk has even diminished, so that it can be said that PL information produces all three possible effects in the same measure.

However, 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.

The fact that no overall increased risk perception can be associated to PL reading, and that nonetheless the presence of specific topic of concern is indeed associated with different risk and benefit perception patterns can be interpreted as a sign of no "spill-over effect":[50] *participants do not take seriously any item of risk information contained in the PL, but only specific items.*

Yet neither the presence of a specific topic of concern nor the change in risk/benefit assessment seem to influence 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 observed in the sample, these data support the hypothesis that the therapeutic decision concerning prescription drugs is rather 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. Think-aloud experiment: the relevance paradox

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 peace 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 leads the single user to consider the text as *constitutively over-informative*.

The key for the selection of relevant information is constituted by two filters:

1. Connection with doctor's information.
2. Counterfactual neglect;

2.1 Connection with doctor's information

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.

[49] Nink, Schröder, 2006: 76.

[50] See Viscusi, Magat, Huber, 1987: 169

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.

PL information which can be connected to what the doctor has already communicated is considered relevant; the remaining data tend to be considered as not personally relevant and are therefore neglected.

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.

2.1 Counterfactual neglect

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 incomprehensibility of words or text passages is 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 peace of information, this means that it does not address me; therefore I can skip it". In this case the conviction is entertained, that *what cannot be understood lies in the doctor's responsibility*.

2.3 Strategies for coping with uncertainty

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. Different strategies to cope with uncertainty are then activated: reappraisal, 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.

The adoption of such biased heuristics and selection filters raises some doubts about the legitimacy of PL information as a risk disclaimer also on empirical grounds.

However, 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 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.

At the end of the investigation, some suggestions for improvements are proposed to the legislator and the text designer.

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?[51]
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 and decision theories.

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.

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[51] See Klemperer, 2003; Jotterand, 2001. Socio-psychological contributions to the debate can be found in van den Brink et al., 2006; Murray et al., 2006; Flynn et al,, 2006; trevena et al., 2006; Woolf et al., 2005; Stalmeier et al., 2005; Steckelberg, 2005; Epstein et al., 2004; Whitney et al., 2003; Coulter et al., 1999; Charles et al., 1999; Gafni et al., 1998; Ubel, Loewenstein, 1997.

– 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.

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.

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 to drug use itself. However comprehensible and well designed no package leaflet could cancel the uncertainty induced by information about side effects. [52]

[52] No matter how readable, comprehensible and well designed, no PL could promise a risk-free therapy: "Trotz aller Bemühungen, die Patienteninformationen besser verständlich zu machen,

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.

Conclusion

This paper has presented the results of an investigation on the legal function, communicative status, normative evaluation and psychological effects of PL information.

The legal analysis identifies two main functions of PL information: warranty of the consumer's right to safety and of his right to choice. Within this second task, PL information comes to be a risk disclaimer in analogy to the information provided by the physician within the institute of informed consent.

The normative evaluation proceeds then in the examination of PL contribution to the accuracy of the risk/benefit prognosis as a measure of decision optimization. It results that PL information cannot provide tailored data as to the risk and benefit probability and is therefore an unreliable basis for the risk/benefit prognosis. Moreover, the lack of any magnitude indexing hinders any appraisal of the risks faced by the drug user because of his incompetence in dealing with medical information in general and in gauging the health implications in the medium-to-long term of some specific side effects. It must be concluded that the therapeutic decision based on PL information rather approaches a decision under ignorance than one under risk. Therefore consent obtained on these grounds should be considered invalid in that it cannot be considered informed.

The empirical analysis shows discrepant phenomena. In general PL information is selected through biased filters and this constitutes an objection to its validity as a basis for informed consent also on empirical grounds.

Finally some suggestions for text improvement and, more importantly, for the legislator are given. In particular, it is proposed to clearly distinguish the safety and the self-determination function of PL information especially in the articulation of liabilities. This distinction would emphasize the consumer's contributory liability in matters of compliance with safety information, and extend strict liability of pharmaceutical firms to relevant damage independently of the tolerability threshold. Such a strategy would stimulate patient's empowerment and pharmaceutical safety at the same time.

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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).

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