Drafting of a Table Guidance on OFF LABEL USE for the ICH – Data Driven Drug Development and Marketing Authorization

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Abstract

Among health care professionals, in particular in Germany, a legal uncertainty as to what medical uses exactly fall under the term of off- label- use is noticeable. The lack of a common definition complicates comparison of methods of resolutions in different countries. A current ambiguity is shown to cause false patient education and invalid informed consent, hence leading to liability concerns.

Health care professionals are in need of drug information to assure safety of treatment, but legislative hurdles may hinder access to information while at the same time broad dissemination of off- label information is considered a risk of circumventing marketing authorization.

The situation described above has motivated to develop in the framework of this research techniques on the model of UK NHS trust's guidance to thus assure safe off- label- use. The chief purposes of this study on the off- label- use practices in Germany are in the short term to:

1) Draft a legal concept for a safe off label use,
2) Draft an off label prescribing, supply and use of medicines policy and
3) Draft guidance for dissemination of information on unapproved uses of medical products.

Additionally for the long term a Drafting of data capturing requirements and Drafting of a mechanism to generate data driven templates or negative pledges on off label use are needed to be considered.

This article describes concrete examples of the German Off- Label- Use Is-situation with regard on the German Drugs Law (AMG) and some juridical decisions (e.g. Nikolausurteil – Federal lawsuit decision from 06.12.2005, Az.: 1 BvR 347/98). It further presents the results of the survey we had conducted in 2013/2014, a concept for safe Off- Label- Use and treatment, based on the recent research works (survey, discussion with the different actors - medical doctors, pharmacists, Health Insurances, Health authorities) for the future, and in particular for enabling more certainty among the health professionals

Keywords: **Off- Label- Use, Drug prescription, Knowledge Data base, German Drugs Law (AMG).**

Actual Off- Label- Use Situation in Germany

Among health care professionals, in particular in Germany, a legal uncertainty as to what medical uses exactly fall under the term of off- label- use is reported. The lack of a common definition complicates comparison of methods of resolutions in different countries.

A current ambiguity is shown to cause false patient education and invalid informed consent, hence leading to liability concerns.

We had conducted in 2013/2014 in scope of this study a survey. Most of the interviewed health professionals, pharmacists, health authorities and

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employees of several pharmaceutical industries consider the Off- Label- Use only as the use of medicine/ drugs for unapproved indication, or in an unapproved age group, unapproved dosage, or unapproved form of administration[1]. The practicing Over- the- Counter- Drugs (OTCs) purchasing and/ or selling linking to the Off-Label- Use, the discount agreement (Discount Agreement: German health care legislatives prescribe discounts on the drugs' price. Every health insurance company has to negotiate with pharmaceutical companies for off- patent and/ or not patented medicines discounts. Pharmacies can then exclusively sell to the patient drugs from the manufacturer's drug with which the fund has entered into a contract. Since July 2014 about 53 percent of all drugs sold with the same agent are covered by health insurance's discount agreement. The benefit to the insured: insurance companies can exclusively provide their insured with molecules concerned without supplement costs.) between Health insurances and the different pharmaceutical groups are mostly ignored. Additionally we can notice a lack of a common definition of the terms of Off- Label- Use among the health professionals and actors. Despite the lack of a common definition Off- Label- Use is widely practiced and is generally "legal" unless it violates some costs reimbursement regulation of the most German health insurances, specific ethical guidelines or safety regulations defined by the German Drugs Law (AMG), but it does carry health risks and differences in legal liability. According to Prof. Dr. med. Jörg M. Fegert, Off-Label- Use and/ or treatment are most frequently practiced in adolescent psychiatry,[2] since most of the psychotherapy- drugs used in the children and adolescents therapy are only approved for adults use. This kind of off- label- use can present for this population risks for the drug therapy. Medical doctors use unapproved medicine and/ or unapproved dosage for the adolescent psychotherapy due to the lack of approved drugs for that age group (adolescent psychiatric patients). Off- Label- Use and/ or Treatment remains an important public health issue for infants, children, and adolescents, because an overwhelming number of drugs still have no information in the labeling for use in pediatrics.[3]

Regulation of Off- Label- Use regarding Administrative Guidelines for Medical Products (AM-RL)

As mentioned above, in Germany, no law **theoretically** prohibits a physician or other healthcare practitioner from prescribing an approved medication for other uses than their specific approved indications (off labeling use).[4] The reality is however complex, since health professionals can, according to AM-RL, be affected by personal liability and/ or subjected to cost recourse process by prescribing off- label- use drugs or providing off- label- use treatment (§ 106 (5b) of the German Social Security Code V - SGB V-). The German administrative Guidelines (AM-RL) had strictly regulated the reimbursement for the costs of medical products and the prescription of off- label- use drugs. Physicians are therefore in a dilemma: On the one hand it is important for them to avoid drug costs recourse by restraining off- label- use prescription, on the other hand they have, regarding to the liability law, to medically treat their patients even with off- label- use drugs and/ or a proper therapy. German physicians are in this situation subjected to financial, economical, professional risks and legal dilemma. Thus each physician is uncertain in any situation where off-label- use drugs/ treatment can or have to be prescribed for better or alternative medical treatment, then when the physician is subjected in a drugs costs recourse process, he cannot oblige the patient beneficiary of the off- label Regulation to pay the drugs costs recourse. The drugs costs recourse may under certain circumstances amount to considerable sum due to expensive, innovative drugs. In some cases, drugs costs recourse therefore can even lead to a financial ruin and insolvency of a medical practice.

According to §35c (1) of the German Social Security Code V (SGB V), the Federal Joint Committee (Gemeinsamer Bundesauschuss - G-BA -) provides and describes in its code of procedures (Chapter 7 § 44: Conditions of prescription of Drugs for Off- Label- Use) a binding administrative regulation and procedures on the scope of the prescription of medicinal products for unapproved indications or applications area. Thus any general physician (GP) or hospital physician is then allowed to use any medicinal products in off- labeling if following conditions, defined by the G-BA, are met:

1. If with the consent of the pharmaceutical industries and according to § 35c(1) SGB V the expert groups recommend the prescription in off- labeling with regard on positive feedback related to the state of scientific knowledge (evidence) about the use of these drugs in unapproved indications or application's area and

2. The Federal Joint Committee (G-BA) has accepted and taken the recommendation in the

German drugs Directives (AM-RL) in its Annex VI part A.

The G-BA determines in § 45 of the Code of Procedures the directives for commissioning the experts groups. It further sets the conditions of the collaboration between the expert groups and the staffed commission at BfArM (Federal Institute for Drugs and Medical Devices - Bundesinstitut für Arzneimittel und Medizinprodukte) in § 46.The process of assessment of medical products subjected to an off- label- use is clearly elaborated in § 46 (5). The point §46 (5)/(9) indicates that the reviews/ evaluation of the application on off-label- use for medical products must include comprehensive information on the following aspects*:....(9) Side effects/ interactions, if they go beyond the approved labeling information or do not be mentioned*

This means that the G-BA looks for evidence before authorizing the use of the given drug in an unproved context. Unfortunately emergency cases are not taken in consideration. Health professionals have to apply for the authorization before they provide an off- label- use treatment or prescribing off- label- use drugs, if the given drug is not already listed on the positive list of the G-BA. A positive list is a database or annex that contains the name of all drugs and/ or treatment the G-BA has authorized in previous authorization application processes to be used outside their specific approved indications. Prescribing such drugs or providing such treatment whose names are containing in the positive list are not prohibited and do not require an authorization again. Health professionals are even not liable in case of health damage or death, if they use or prescribe the drugs accordingly to the recommendation of G-BA. G-BA had also regulated the reimbursement of such drugs authorized to be prescribed for unapproved indication. Health professionals can therefore not be subjected to drugs costs recourse or re-taxation. A question remains here open, namely **who is in case of an authorized off- label- use liable for any damage the medical product can cause?** The AM-RL does answer this question. According to the German Drugs Law (AMG) § 84 (1) the pharmaceutical manufacturer is liable for any health damage the intended use of a drug causes

Legal Liability and Uncertainty among the Physician

Health care professionals are therefore in need of drug information to assure safety of treatment, but legislative hurdles may hinder access to information while at the same time broad dissemination of off- label information is considered a risk of circumventing marketing authorization.

Off- Label- Use is widely practiced in all areas of the medicine. Unfortunately due to the legal uncertainty, the risk of financial ruin and insolvency and the possible legal liability for the health practitioner in case of health damage, most of the health professionals do not accept having practiced it. In fact the patient would not be well educated or informed. Health professionals can thus also intentionally "falsify" one's diagnose in order to prescribe to him legally off- label- drugs or treatment and thus avoid to be subjected to any costs recourse process or be liable in case of health damage.

It's therefore important to define some solution approaches and techniques on the model of UK NHS trust's guidance to thus assure safe off label use in German context.

Reimbursement of Off- Labeling medical claims

- **Legal Context**

  Health professionals can, according to AM-RL, be affected by personal liability and/ or subjected to cost recourse process by prescribing off- label- use drugs or providing off- label- use treatment (§ 106 (5b) and § 135 (1) the German Social Security Code V- SGB V-). However, according to § 137c. (1) SGB V (German Social Code V) this rule is not applicable to hospitals and clinics. In hospitals off- label- use drugs can be prescribed off-label or new unapproved treatment can also be provided and resultant medical claims can be submitted to the health insurance, as long as they have not been excluded by the G-BA from liability (so- called "authorization subjected to prohibition"), while new treatment methods in the outpatient care area can, accordingly to § 135 (1) SGB V, only be provided at the expense of the health insurance, if the methods have been recognized by the G-BA. Prerequisite for entitlement to the benefit of the hospital is rather that the inpatient hospitalization is medically necessary. Furthermore privately insured patients are not concerned with these issues, since the compulsory treaty indemnity of the Private Health Insurances (PKV) allows "alternative medical treatment methods – e.g.

homeopathy" linking to and usually includes Off- label- use. Also in stationary applications (inpatient treatment) off- label- use is allowed and thus the hospitals cannot be subjected to costs recourse process, then all therapy costs beyond the case- based lump sum (DRG) - and therefore any (additional) cost for an off- label- use – would not be reimbursed by the health insurance but are borne by the hospital.

- **Important Lawsuits and Juridical Decisions**

Judgment/ Decisions of German Federal Social Court (BSG) on 19th of March 2002, Ref.: B 1 KR 37/00 R

The German Federal Social Court (BSG) had answered to the question of when a German statutory health insurance (GKV) and private medical insurance (PKV) can be committed to reimburse Off- label- use drugs and/ or treatment. The Court has in its judgment of 19 March 2002, Ref.: B 1 KR 37/00 R recognized the need for a restricted Off- label- use under following strict conditions:

The prescription of a drug for unapproved indication can therefore only be considered:

1. For the treatment of a serious (life- threatening or quality of life in the long lasting debilitating) illness

2. If no other therapy is available, and if

3. Admissible and scientifically proven evidence is available and announces that a successful treatment (curative or palliative) can be achieved by using the medical product concerned or providing the (new) unapproved treatment methods concerned. Further, it can be assumed that the present suggested unapproved treatment methods or drug indication may be approved for that indication - extension of approval has already been applied and the results of a controlled clinical trial of phase III (against Standard or placebo)

Judgment/ Decisions of German Federal Constitutional Court (BVG)) on 6th of December 2005, Ref.: BVerG 2005 AZ 1BvR 347/98l

On 6th of December 2005 the German Federal Constitutional Court (BVG) had eased in its judgment Ref.: BVerG 2005 AZ 1BvR 347/98 (so-called Nicholas judgment) the restriction of BSG judgment as follows:

Off- label- use drugs or (new) unapproved treatment are allowed in case of:

1. Life- threatening or fatal regularly disease

2. No generally accepted medical standards appropriate treatment available

3. Serious indications on a possible healing success or significant positive effect stopping the disease progression.

Additionally, the judgment from 3rd of November 2006 (Ref.: BvR 3101/06) had clarified the point concerning "life- threatening or fatal regularly disease". This judgment conducted to an important change by introducing on 20th of December 2011 into the SGB V the § 2 (1a) that enables off- label- use in case of life- threatening or fatal diseases.

Table 1 shows the difference between the two important juridical decisions about off- label- use and reimburse ability of off- label- use.

The judgment (BVerG 2005) had extended the previous judgment and eased the conditions of reimburse ability of off- label- use and/ or unapproved treatment.

BSG 2002	BVerG 2005
Severe diseases	**Life- threatening and/ or fatal diseases**
• Perspectives on a Successful Treatment	• Perspectives on a Successful Treatment
• No Alternative, approved therapy is ineffective or not tolerated	No generally approved medical treatment is available

Table 1.Comparison of two important juridical decisions on off- label- use

Judgment/ Decisions of Frankfort Social Court on 28.08.2006 Ref. S 21 KR 444/06 ER

In 2006 (22.08.2006) the Frankfort social court had accepted a patient lawsuit (S 18/4 KR 571/05) against a health insurance. Patient mentioned in the lawsuit that his health insurance rejects the medical claims because the practitioner uses an unlicensed drug (Interferon Alfa-2a) during the treatment. The used drug does not have a

marketing authorization for the German market and is thus unapproved drug for any treatment in Germany. Based on the previous judgments (see table above) the court obligate the health insurance to pay the medical claims. This judgment has extended the all the previous judgment, since it authorizes the use of unlicensed drug within any treatment accordingly to the juridical decisions of BSG and BV, and the insurance has to pay the medical claims.

Despite the decision (interim order) of the Frankfort Social Court on 31st October 2005 obliging the health insurance to assume the therapy costs, the health insurance argued during the principal proceedings that the disease concerned does not fit the conditions defined by several previous judgments, in particular, the decision of the BVG. It had therefore asked the court to reject the patient's lawsuit. The court confirms in the final judgment its decision from 31st October 2005.

Proven Evidence is Mandatory: Off- label prescriptions must better serve patient needs than alternatives and must be supported by evidence or experience to demonstrate safety and efficacy. Unfortunately there is often little or no proven evidence of efficacy on much use of drugs for unapproved indications. A regulatory review of the benefits and risks of using the drug for unapproved indication has mostly not taken place. The lack of proven evidence of efficacy or reported experiences in dealing with off- label- use drugs represents potential hazards for the patient with the legitimate desire of an effective treatment, since the drugs are not sufficiently tested. Nevertheless the use of medical products for unapproved indications is seen as an essential part of the therapies in oncology, neurology and pediatrics. However, severe and very severe side effects that can lead to deaths due to drugs used for unapproved indications are reported. It is then important for patient's safety and protection drugs should only be used accordingly to the German Drugs Law (AMG), German Social Code (SGB) and the juridical decisions of the Federal Social Court (BSG).

Most juridical decisions reject patient lawsuit against health insurances which refuse to assume the therapy costs in case of off- label- use. The AM-RL has provided a guideline for the use of drugs for unapproved indication in order to assure safe off- label- use and protect the patient from any health damage (Chapter 7 § 44: Conditions of prescription of Drugs for Off- Label- Use). Proven evidence is therefore mandatory for a safe off-label- use practice.

Research Objectives

In the framework of this regulatory research work it is expected to measure the following:

- **Comprehension and understanding off-label use using Delphi technique:** Delphi technique is an experimental study of group opinion, establishing similarities and differences between definitions and Forecasts the future development of understanding. It further identifies characteristics of off label use, establishes consensus for off label criteria, compares results obtained using two expert panels for validation and provides group judgment for a subject matter. [Definition of Department Drug Regulatory Affairs] The Delphi technique had been modified to fit with the needs of regulatory research in order to measure in- depth understanding of the terms of off- label- use.
- **Success and Efficiency of policies regulating off label use:** Off- label- use policies and regulations were sought after and evaluated. Discussions with experts were conducted and have provided in- depth understanding of purposes of certain laws directives. Public opinions on the topic were needed and asked.
- **Validity and effectiveness of advertisement regulations:** Juridical decisions have been evaluated and notices of defect will be presented. Beyond, costs of unit per annum were quantified. However in the framework of this study sponsors and refunding were not classified also cost- performance analysis were not performed. This will be subject of our forthcoming article.

Survey and Results

Methodology

Research methods used in the framework of this study consist of comparison of approaches, juxtaposition of the different definitions and presentation of concepts. Delphi survey technique was chosen and used for gathering data and information. A Delphi survey has already been used to develop common definitions for unlicensed and off- label drug use for research and regulatory purposes in the past by Neubert et al., but to be used only for pediatrics.[5] Web- based application, a questionnaire have been designed (http://www.surveymonkey.com/s/JFGKJVY) and

used to interview representative roles from industry, medical and pharmaceutical society associates, regulators, health insurance associates and academia. Additionally paper based questionnaires in German had been sent to the health professionals; telephone interviews and face- to- face discussion had been conducted considering the Delphi survey technique (fig. 1). Delphi surveys involve a number between three and ten experts in a particular area and three or four occasions. The first interview is an open-ended discussion on participants' opinions. Findings are synthesized and reported back to the interviewees prior to a second round discussion. Responses are kept anonymous for reasons of privacy and biases. The level of agreement to the finding, any modifications or refinements as well as points of disagreement is upraised. This is repeated a minimum of three or a maximum of eight times or until consensus on the key predictions. Consensus was defined as a qualified majority of 2/3 (66.7%) in all responses.

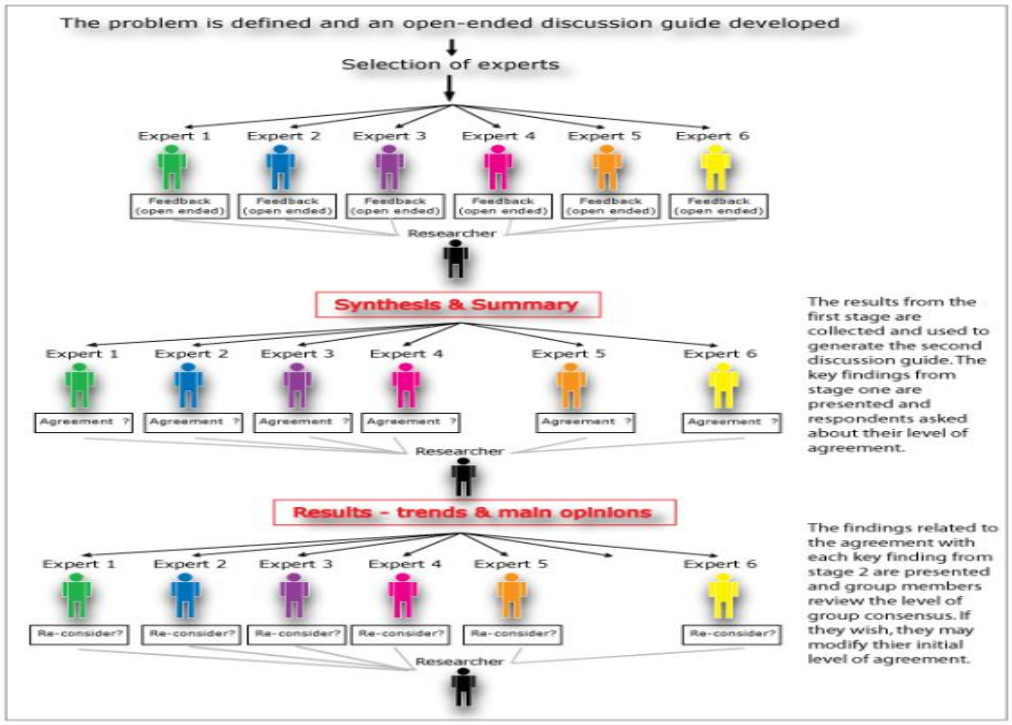

Figure 1.Business dialogue insight to action (ed.) The Delphi Technique and B2B marketing research. Available at http://www.dialogue.biz/PRINTarticle012.htm, as to 24.07.2009

Interview

Duration of the survey: 01.2012 - 02.2013 we interview:

- 33 organizations contacted by letter, phone, Email (100 % participation).
- 6 hospitals contacted by questionnaire (Rechts der Isar, University Hospital Cologne, etc.) 1 written reply.
- 12 General Practitioners in Bavaria: No reply.
- 16 Associations.
- Und

Conclusion: Good cooperation with the organizations, Low participation of individual physicians.

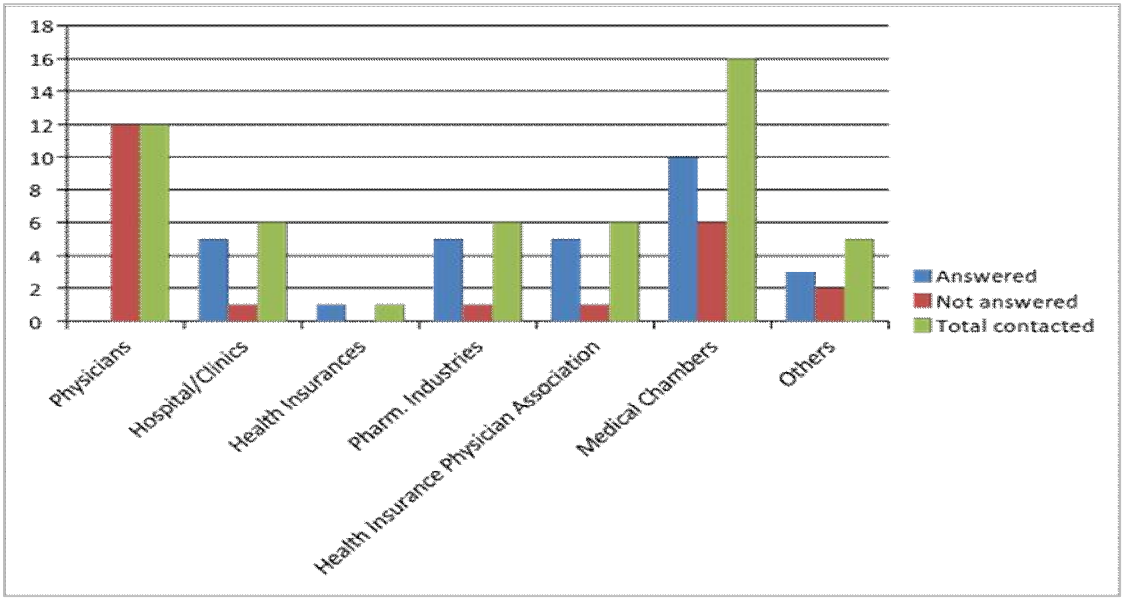

Figure 2.Structure of the interviewees

Federal State	Categories of Interviewees
Bavaria	Hospital/ Clinic
	Health Insurance Companies
	Association of Statutory Health Insurance Physicians
North Rhine- Westphalia	Hospital/ Clinic
	Pharm. Company and similar
	Association of Statutory Health Insurance Physicians
	Medical Association
Baden- Württemberg	Hospital/ Clinic
	Association of Statutory Health Insurance Physicians
	Medical Association
Saxony	Association of Statutory Health Insurance Physicians
	Medical Association
Lower Saxony	Association of Statutory Health Insurance Physicians
Berlin	Hospital/ Clinic
	Medical Association
Hamburg	Medical Association
Saxony- Anhalt	Medical Association
Thuringia	Medical Association
Saarland	Medical Association
Schleswig- Holstein	Medical Association
Rhineland- Palatinate	Medical Association
Brandenburg	Medical Association
Mecklenburg- West Pomerania	Medical Association
Federal Level	Federal Health Insurance Association
	Federal Physician Association
	G-BA
	Federal Institute for Drugs and Medical Devices

Table 2.List of the interviewees

Questionnaires

- **Definition of the terms**
  - **Proposed Definitions (according to the literatures)/ Questionnaires**
    - **Off- Label- Use**

D1: An Off- label- use is understood as applying unapproved (new) medical treatment methods or techniques and/ or using an approved drug with national marketing authorization and/ or EU approval for unapproved indication (different age, dosage, weight, etc.), particularly the application of an authorized medical product beyond national or European the regulatory.

D2: An Off- label use is when prescribing (approved) drugs for unlabeled diseases – the disease concerned is not indicated in the product information or package.

D3: Off- label use is the use of drugs beyond the drug legally approved indication.

● Unlicensed Use

D1: Is the use of a medicament for the treatment of adults and children, which has no national market approval and/ or no European market approval.

D2: Unlicensed Use is described as the use of unapproved Drugs such as molecule, extemporaneous without clinical trials, Import drugs without marketing authorization the country concerned or approval

● Compassionate Use

D1: Compassionate Use as the application of a potentially effective but not yet approved drug in individual cases (e.g. for patient in life- threatening or fatal situations) or for not otherwise treatable diseases in the context of compulsory medical treatment and therapeutic freedom.

D2: Compassionate use is understood as, considering the human aspects, providing to a group of patients, suffering from a debilitating chronic or fatal illness or whose disease is considered to be life-threatening and cannot be treated satisfactorily by an authorized medicinal products

● Orphan Use

D1: is used for treatment of rare diseases

Results

Domains	Definition	Results
Off- Label- Use	D1	Hospitals and pharmaceutical industries adopt this definition
	D2	None
	D3	None
Unlicensed Use	D1	None
	D2	None
Compassionate Use	D1	None
	D2	None
Orphan Use	D1	None

Table 3.Results on Definition's questionnaire

- **Comprehension and understanding off-label among the health professionals**
  - **Questionnaires:** See annex.
  - **Policies regulating off label use:** This questionnaires' category concerns essentially the administrative directives (e. g. AM-RL des G-BA \$8, \$9 und \$16) See annex for details.
  - **Advertisement regulations:** See annex.

Results and Capturing Information/ Data

The survey and discussions with the different stakeholders had enabled us to measure how is their in- depth understanding of the terms of off-

label- use. Discussions with experts were conducted and have provided in- depth understanding of purposes of certain laws directives. Juridical decisions and/ or judgment had been analyzed. Thus we can affirm that the most disputes and conflicts also misunderstanding on the term of Off- Label- use are more financial than patient protection problems. Since according to the AM-RL directives, hospitals are not prohibited from prescribing or providing Off-Label- Use and/ or unapproved treatment. However this has not to lead to additional costs for the health insurance Companies [case- based lump sum – DRG -]. Further we can notice that doctors are asking for more legal framework and liability protection and are uncertain on the term. Their low participation shows the uncertainty degree among them (the medical doctors).

The concept we presented and discussed with some hospitals and other health professionals was significant supported and accepted. We thus collected significant data, information, and opinions that we analyze. The analysis helps to perform our concept. The capturing data, information and opinion concern the judgment, advertisement regulations, regulations and directives of off- label- use and the degree of in-depth understanding of the term among the health professionals.

General Problem and Capturing Data Analysis

Comprehension and Understanding of Off-Label- Use

We like to analyze the current German off- label-use situation in viewpoint of:

- Law
- Computer Sciences (Information gathering)
- Patient's safety and protection
- Legal liability

- **Reimbursability and Legal Liability**

The amount of patients' lawsuits and juridical decisions (Table 2) show an uncertainty regarding the term of off- label- use in Germany. During our research work we noticed that health insurance companies mostly refuse to assume any off- label-use therapy costs when outpatient is concerned. They refer to some judgment (in the case of the use of "Interferon" - Judgment/ decisions of Frankfort Social Court on 28.08.2006 Ref. S 21 KR 444/06 ER – the health insurance concerned argued with the decision of the judgment BSG/B 1 KR 37/00 R, BSGE 89, 184 ff from 19.03.2002-).

As described above off- label- use treatment in case of hospitalized inpatient is allowed as long the costs of any off- label- use therapy not extend the case- based lump sum (DRG) - and therefore no (additional) cost due to an off- label- use therapy for the health insurances.

The legislative and administrative hurdles may hinder to assure safe off- label- use, since the G-BA needs more proven evidence before authorizing drugs in unapproved indication. In one hand proven evidence is mandatory for any application for off- label- use authorization. In other hand the German Drug Law (AMG) regulates strictly the clinical trial which can only be initiated and/ or conducted by a pharmaceutical manufacturer (§§40-42a AMG). To extend the indication of an already authorized medicinal product, the pharmaceutical manufacturer has to provide new clinical trials of phase II and III (AMG).[6,7,8] However pharmaceutical manufacturers would not spend amount of sum to extend some of their drug's indication or to provide evidences for any off- label- use of those drugs that are already authorized for sale. Therefore only the practitioner can provide some evidences for drugs to be used for unapproved indications. During our research we had not noticed a case for which a pharmaceutical manufacturer extends drugs indications to facilitate an off- label- use. If drug indications are extended and it is used for the extended approved indication, then this drug is no longer more an off-label- use drug for the concerning indication. Therefore proven evidences can only be provided for drugs for unapproved indications. Only in this case we can use the term of off- label- use. Evidences have to be provided by health professionals at hospitals or GP practices. Unfortunately the health professionals are facing a legal uncertainty due to their liability in case of health damage and costs recourse process. How can they, regarding these legal uncertainty and legislative hurdles, provide evidences? It is well known that any use of drug for unapproved indications has to be authorized by the G-BA in order to be reimbursable, to protect the patient from any health damage and/ or death and also the practitioner won't be liable in case of health damage. Only health professionals working at hospitals can provide proven evidences for drugs use for unapproved indications. Unfortunately

most of the interviewed health professionals during a survey in scope of this research work do not accept officially having used drugs for unapproved indication. However they recognize that off- label- use is widely practiced at the hospitals, clinics and by GPs. No one reports the results of those uses which could set a benchmark for the off- label- use of the drug concerned.

Dates	Court	Decisions References
26.09.2006	BSG	B 1 KR 1/06 R Rz. 15
19.03.2002	BSG	B 1 KR 37/00 R
31.05.2006	BSG	B 6 KA 53/05 B.
09.02.2011	BSG	B 6 KA 53/10 B
19.10.2004	BSG	B 1 KR 27/02 R
06.12.2005	BverfG	1 BvR 347/98
04.04.2006	BSG	B 1 KR 7/05 R.
14.12.2006	BSG	B 1 KR 12/06 R.
26.09.2006	BSG	B 1 KR 14/06.
26.09.2006		B I KR 1 /06, Rz. 18. (decision on Ilomedin)
15.03.2005	BGH	VI ZR 289/03.
29.06.1995	BGHSt	4 StR 760/94;
21.04.1999	OLG Saarbrücken,	1 U 615/98-112
05.12.2005	SG Berlin	S KR 219/05
31.05.2006	BSG	B 6 KA 53/05 B
09.05.2006	LSG Schleswig- Holstein	L 4 KA 14/04

Table 4.List of juridical decisions concerning the off- label- use

- **Patient's Safety and Protection**

According to a report of Priv. Doz. Dr. med. H.E. Langer on 04.02.2002, Paul- Ehrlich- Institute has reported about 29 death cases registered till to 31st of December 2001 in Germany due to the use of **Remicade (Infliximab)**. The institute has further reported that 10 death cases among the 29 death cases occurred because of the use of the drug concerned for unapproved indications (off- label- use).[18] Since most of off- label- use treatments are not documented it is difficult to show how off- label- use drugs can also cause health damage for the patient. The health bodies have to find solutions and the ways to protect the patient on one hand and on other hand enable the patient to be treated in case when off- label- use drugs are the last possibility to provide a possible successful treatment. Therefore regulations are needed to help the patient, protect him by preventing illegal Clinical trial. Thus this can cause false patient education and invalid informed information in case of successful off- label- use consent. More important is the loss of important evidence If health professionals may "illegally" prescribe off- label- use in order to avoid costs recourse process and any liability, so they could be punished by the law in case of health damages.. We can then conclude the different legislative, administrative guidelines hurdles and reimbursement politics of the health insurance companies hinder on one hand to provide enough evidence for off- label- use drugs and on other hand increase the uncertainty among the practitioners, but increase the patient protection against possible health damages or death by using unproven off- label- use drugs.

- **Uncertainty among the Health Professionals**

Why health professionals are so uncertain on the terms of off- label- use and others? In viewpoint of information technology, the health professionals lack of information about evidences or experiences about off- label- use drugs. Beyond, the AM-RL directives on the authorization application increase the uncertainty among them.

- **Success and Efficiency of policies regulating off label use:** The analysis of the success and efficiency of policies regulating off- label- use will be subject of our forthcoming article.

- **Validity and effectiveness of advertisement regulations#:** Subject of our forthcoming article.

Quantification of the costs of unit per annum

Sponsors and refunding classification also cost-performance analysis regarding the practice of off-label- use will be subject of our forthcoming article.

Solution Approach and Table Guidance on Off- Label- Use

Recommended Common Definition

According to the results of our survey we recommend the definitions below to be adopted as common definition for the following terms:

- **Off- Label- Use:** A common definition of the term of off- label- use has to consider the following aspects:
- **The Indications and dosage** for an unapproved use
- **The Age/ Age group**
- **The Form, methods, and duration** of the application. Further it's important to consider how the patient privately uses the drugs (for. Ex. If he strictly follows the indication as the time, quality of water to be used, after or before a meal etc.)
- **Marketing Authorization**: No marketing authorization for German market or no EU approval (Unlicensed Use/ No- label- use)
- **Worldwide Approval**: No approval exists yet worldwide; but experience from clinical trials are available/ existent (compassionate use)
- **Marketing Authorization Expiration**: the product has no longer authorization because it is expired or withdrawn
- **The Over the Counter Drugs**: The OTC practice in pharmacies due to Discount agreements with the health insurances

We therefore propose following definition as common with regard on the criteria listed above:

An Off- label- use is understood as applying unapproved (new) medical treatment methods or techniques and/ or using an approved drug with national marketing authorization and/ or EU approval for unapproved indication (different age, dosage, weight, etc.) or for unlabeled diseases (the disease concerned is not indicated in the product information or package), particularly the application of an authorized medical product beyond national or European the regulatory and/ or beyond the drug legally approved indication and administrative directives such as: (1) Expiration of the marketing authorization, (2) No worldwide Approval for the drug or treatment concerned, (3) OTC- Drugs, (4) generic medicinal products due to discount agreement between pharmaceutical industries and health insurances

- **No- Label- Use and Unlicensed Use:** Unlicensed Use is the use of a medicament for the treatment of adults and children, which has no national market approval and/ or no European market approval. However unlicensed use of medicinal products has to be considered on two levels: (1) No- Label Unlicensed Use and (2) Off- Label Unlicensed Use.

  No- Label Unlicensed Use is defined as the use of Import approved Drugs, molecule, extemporaneous with marketing authorization, however without marketing authorization (without clinical trials) in the country concerned and/ or no EU approval for the approved indication providing medicinal treatment to a group of patients, suffering from a debilitating chronic or fatal illness or whose disease is considered to be life-threatening and cannot be treated satisfactorily by an authorized medicinal products. Off-Label Unlicensed Use is the use of No- Label Unlicensed drugs for unapproved indication

- **Compassionate Use:** Compassionate Use as the application of a potentially effective but not yet approved drug without proven clinical trials in individual cases (e.g. for patient in life- threatening or fatal situations) or for not otherwise treatable diseases in the context of compulsory medical treatment and therapeutic freedom.

- **Orphan Use:** is used for treatment of rare diseases.

Improving the Legal Circumstances to assure Secure Off- Label- Use

- **Increase the certainty among the Health professionals:** We recommend regarding the existing off- label- use directives and administrative guidelines (in case of Germany AM-RL) following changes for an increased certainty among the health professionals:
- Same rule/ directives for in and hospitalized outpatient regarding the off- label- use reimbursement regulations (costs resources)
- Less liability for health professionals. The health system has to produce more evidences and provide the health professionals with more information about off- label- drugs. In case of health damage or death Physicians shall not be liable because of off- label treatment, but because of wrong treatment. Off- label- use and approved treatment shall thus be coequal regarding the Drugs law.
- The pharmaceutical companies have to be legally more involved into the Evidence capturing processes.
  It shall be possible for the pharmaceutical companies to use the proven evidences' findings to extend drugs' indications without applying for a new mandatory marketing authorization. More collaboration between pharmaceutical companies and practitioners have to be encouraged. Scientifically proven Evidences shall be accepted as clinical trials phase 2 and 3 and thus lead to indications extensions.
- Define a clear reimbursability politic for the off- label- use: AM-RL directives on costs recourse in case of off- label- drugs have to be suppressed, thus practitioners should not anymore be subjected to costs recourse process. Also all off- label- therapies' costs shall be case- based lump sum for the outpatient treatment too.

- **Ease the Drug Law (§§ 40) regarding the extension of Indications**

Improving the prescription policies

A sample of off label policies of British NHS trusts shall serve as a model for guidance to health care professionals. Items shall be identified from the policies and tested for feasibility. Therefore, a survey with a web- based questionnaire will provide evidence for practicable management of off label use among health care professionals, attorneys and regulatory professionals.

The description of improved prescription policies will be subject of our forthcoming article.

Enabling Evidence gathering

Mandatory Reporting requirement for all off- label- use/ - treatment: All off- label activities (with positive or negative results) must be mandatorily reported. This means a high legislative certainty among the health professionals and less liability in case of health damage has to be provided for the health professionals. It is further important to prevent the health against any costs resources process after practicing an off- label- use/ treatment. Soon those conditions listed above are met; it will be easy to capture more data about the off- label- use. In viewpoint of computer sciences we propose some tools to ease the data capturing and data analysis.

- **Knowledge- Database (KDB) for a safe Off- Label- Use**

KDB is a system designed for collecting data and data analysis. This system is based on technologies like data warehousing (data capturing) and data mining and/ or data analysis (a process used by companies to turn raw data into useful information. By using software to look for patterns in large batches of data, businesses can learn more about their customers and develop more effective marketing strategies as well as increase sales and decrease costs. Data mining depends on effective data collection and warehousing as well as computer processing. http://www.investopedia.com/terms/d/datamining.asp). Data mining is the analysis of data for relationships that have not previously been discovered.[9] The KDB system is further consisting of a mechanism for generating pattern lists of off- label- drugs and treatment with high evidence and evidence based knowledge on Off- Label- Use in order to help or assist the health professionals

Depending on the legislative situation regarding the off- label- use we propose two data capturing methods by using our web based user interface: (i) an anonymous (online) off- label- use data capturing and (ii) logged- in (online) off- label- use data capturing with grant access for physicians only.

A Business Intelligence System (according to CIO, business intelligence as a discipline is made up of several related activities, including data mining, online analytical processing, querying and reporting. Companies use business intelligence to improve decision making, cut costs and identify

new business opportunities. Business intelligence is more than just corporate reporting and more than a set of tools to coax data out of enterprise systems. Chief information officers use business intelligence to identify inefficient business processes that are ripe for re- engineering. (http://www.ask.com/business-finance/data-mining-vs-business-intelligence-278d8f619f678338), as backend system of our proposed kDB will take the source of the capturing data in consideration by generating evidence data after automatic analysis of the collected data.

The KDB provides the User with following functionalities:

- **A module for treatment tracking:** This module is a journal where the physician can track how the treatment goes on and documents the methods, the used drug and indication
- **A forum for discussing with another health professionals or pharmaceutical companies**: A discussion forum, where the physician can discuss on a case or advise another physician, also to report a case or reply to a question
- **Search option**: search for proven and/ or succeeded treatment methods, off- label-drug for given diseases, etc.
- **Reporting tools**: At end of the treatment, the physician can use this module to report to the central system his experiences and thus described the treatment and the method concerned also the drugs and indications used. The system will provides the User with a well- defined form and questions to help the physician to provide all need information.

- **More Publication in Scientific Revues**

The generating evidences data (information about collected treatment or off- label- drugs, etc.) would periodically be published in many (paper based and electronic) scientific revues/ journals.

Issues and Open Questions

The analysis of the success and efficiency of policies regulating off- label- use will be subject of our forthcoming article.

Sponsors and refunding classification also cost-performance analysis regarding the practice of off-label- use will be subject of our forthcoming article.

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