Skinny labelling

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AABG	Arzneimittelausgabenbegrenzungsgesetz
ANDA	Abbreviated New Drug Application
API	Active Pharmaceutical Ingredient
BGH	Bundesgerichtshof (German for “Federal Court of Justice”)
BIRPI	Bureaux Internationaux Réunis pour la Protection de la Propriété Intellectuelle (French for “United International Bureaux for the Protection of Intellectual Property”)
CMDh	Co-ordination Group for Mutual Recognition and Decentralised Procedures - Human
CP	Centralised Procedure
CRP	C-reactive protein
DCP	Decentralised Procedure
EC	European Community
EEC	European Economic Community
EMA	European Medicines Agency
EU	European Union
CFR	Code of Federal Regulations
EPC	European Patent Convention
EPO	European Patent Office
EU	European Union
FDA	Food and Drug Administration
FD&C	Food, Drug and Cosmetic Act
GAD	Generalised anxiety disorder
GATT	General Agreement on Tariffs and Trade
G-BA	Federal Joint Committee (Gemeinsamer Bundesausschuss)
HCV	Hepatitis C virus
HeFH	heterozygous familial hypercholesterolemia
HoFH	homozygous familial hypercholesterolemia
ICU	Intensive Care Unit

IND	Investigational New Drug Application
INN	International Nonproprietary Name
IP	Intellectual Property
MEB	Medicines Evaluation Board
m.n.	margin number
MRP	Mutual Recognition Procedure
NCE	New Chemical Entity
NDA	New Drug Application
NHS	National Health Service
RLD	Reference Listed Drug
SGB	Sozialgesetzbuch (Social Insurance Code)
SmPC	Summary of Product Characteristics
SPC	Supplementary Protection Certificate
USA	United States of America
USC	United States Code
USPTO	United States Patent and Trademark Office
WIPO	World Intellectual Property Organization
WTO	World Trade Organization

1. Introduction

1.1 Historical background

Due to hazardous events with unsafe medicines new systems of drug control were established in Europe and the USA to ensure that only safe medicinal products were put on the market. In the USA, the Federal Food, Drug and Cosmetic Act was enacted in 1938, which is still the basis for drug regulation today. In Europe, the Directive 65/65/EEC was adopted in 1965, establishing a marketing authorisation and basic requirements for medicinal products in most European countries. After several more guidelines were adopted in the following decades, Directive 2001/83/EC established the European pharmaceutical legislation for human pharmaceutical products of today. Since all directives have to be transformed into national law, there are still national differences throughout Europe.

Along with these regulatory requirements, the national health systems have developed. As more and more medicinal products had been authorised and launched, the national health authorities focused on reducing the exploding costs of health care systems. To provide safe and efficient medicinal products at a lower price as branded innovator medicines, the generic industry evolved. This industry successfully offers lower prices than branded innovator medicinal products due to lower development costs as a result of referring to preclinical and clinical data of the innovator.

1.2 Focus of this master thesis

Finding new uses for known substances is a great benefit for the improvement of public health. Patents in form of second medical use claims were established to promote and incentivise this kind of research. Since 2004, it is possible in Europe to market generic medicinal products with carve-outs of patent protected indications or other new uses in their labelling (so-called “skinny labelling”) which are approved only for non-protected indications/uses but are dispensed actually for all indications of the brand medicine in many countries. In this master thesis an overview of the current system regarding skinny labelling is presented. Problems arising out of the current practices are discussed and opportunities for an improvement are proposed by a comparison to the US system and by taking into account the recent jurisprudence concerning second medical use claims.

1.3 Legal basis for marketing authorisations of generic medicinal products

Marketing authorisation procedures of medicinal products are governed by national regulations and international conventions. They are harmonised to a large extent in Europe, USA and Japan, but there are still differences. In Europe, medicinal products can be authorised nationally, simultaneously in more than one Member State via the decentralised procedure (DCP; if the medicinal product has not been authorised before in any of the

Member States) or the mutual recognition procedure (MRP; if the medicinal product has been authorised nationally before in a Member State). The legal basis for both procedures is Directive 2001/83/EC [1]. According to Regulation (EC) No. 726/2004 [2], a medicinal product can also be authorised via the centralised procedure (CP). By this procedure, one application to the European Medicine Agency (EMA), if approved, leads to a marketing authorisation in all member states.

1.3.1 Legal basis for a marketing authorisation for a generic medicinal product in the European Union (EU)

Article 6(1) of Directive 2001/83/EC as amended [1] states:

> *"No medicinal product may be placed on the market of a Member State unless a marketing authorization has been issued by the competent authorities of that Member State in accordance with this Directive or […] with Regulation (EC) No 726/2004…".*

A prerequisite for a marketing authorisation is proven quality, safety and efficacy as well as a positive benefit-risk ratio of the medicinal product.

For Europe, marketing authorisation applications for generics are based on Article 10 of Directive 2001/83/EC as amended and Article 6 of Regulation (EC) No 726/2004 [2]. According to Article 10(1) of Directive 2001/83/EC the applicant

> *"shall not be required to provide the results of pre-clinical tests and of clinical trials if he can demonstrate that the medicinal product is a generic of a reference medicinal product which is or has been authorised under Article 6 for not less than eight years in a Member State or in the Community."*

A generic medicinal product is defined in Article 10 (2) (b) therein as

> *"a medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies. The different salts, esters, ethers, isomers, mixtures of isomers, complexes and derivatives of an active substance shall be considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy."*

The reference medicinal product can be the European reference product, which is not always similar to the national reference product.

1.3.2 Legal basis for a marketing authorisation for a generic medicinal product in the USA

The Federal Food, Drug and Cosmetic Act (FD&C Act) is the basic food and drug law of the USA. FD&C Act Chapter V deals with Drugs and Devices. This chapter is further sub-

divided in Part A to F with Section 501 to 524 containing §§ 351 to 360(n)) [3]. Further legislation can be found within the Code of Federal Regulations (CFR), which is the codification of the general and permanent rules and regulations published in the Federal Register by the departments and agencies of the Federal Government. It is divided into 50 titles. Title 21 contains most of the regulations pertaining to food and drugs [4].

As in Europe, for approval the medicinal product must have a proven quality, safety and efficacy for the intended use as well and its health benefits must outweigh its risks. But the authorisation process in the USA starts much earlier, basically with the submission of the first clinical trial application (Investigational New Drug Application, IND), which is part of the New Drug Application (NDA) [5].

The FD&C Act was amended by the Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Amendments) [6]. These amendments created the modern system of generic drugs in the USA by providing the regulatory framework. The new Section 505(j) established the abbreviated new drug application (ANDA) approval process, by which generic versions of previously approved innovator medicinal products could be approved without submission of a full new drug application (NDA) as is needed for medicinal drug products containing a new chemical entity [7]. Instead of including preclinical and clinical data to prove safety and efficacy, the ANDA refers to these data of the NDA of the innovator medicinal product and provides own data demonstrating bioequivalence. Section 505(j) of the FD&C Act together with 21 CFR 314.94 of the CFR are the legal basis for the marketing authorisation application of a generic medicinal product in the USA [8, 9]. The FDA lists approved medicinal products that may be referenced in an ANDA in the Approved Drug Products with Therapeutic Equivalence Evaluations (the Orange Book).

The term “generic drug” is not used in neither the FD&C Act nor the CFR. Instead, 21 CFR 320.1 speaks of “pharmaceutical equivalents” [10], which have to contain the same active ingredient(s), are of the same dosage form and route of administration and are identical in strength or concentration but can differ in characteristics such as shape, release mechanism, labelling (to some extent), and excipients. A generic drug is defined by the FDA [11] as

> *“A generic drug is the same as a brand name drug in dosage, safety, strength, how it is taken, quality, performance, and intended use. Before approving a generic drug product, FDA requires many rigorous tests and procedures to assure that the generic drug can be substituted for the brand name drug. The FDA bases evaluations of substitutability, or “therapeutic equivalence”, of generic drugs on scientific evaluations. By law, a generic drug product must contain the identical amounts of the same active ingredient(s) as the brand name product. Drug products evaluated as “therapeutically equivalent” can be expected to have equal effect and no difference when substituted for the brand name product.”*

1.4 Intellectual Property Rights

On average, it takes more than 13 years to develop a prescription medicinal product with a new active pharmaceutical ingredient (API) that gains market approval and this development process costs the innovator about 1.0 to 1.6 billion dollars [12]. A new study published by the Tufts Center for the Study of Drug Development in November 2014 speaks of even 2.6 billion dollars [13]. Out of 5,000 to 10,000 substances tested, only one will be marketed [12]. Thus, keeping a pharmaceutical company continuously on a profitable level is a challenging task.

To recover their investment for development and research the pharmaceutical industry and especially the innovator pharmaceutical companies relies upon intellectual property (IP) rights including patents as well as other forms of protection, e.g. exclusivity provisions like data exclusivity or market protection. These protective measures give the innovator company an exclusive, time-limited market access after approval of the innovative medicinal product by the health authority. These incentives are a substantial prerequisite for investments of the innovator companies in time- and money-consuming research and development of new medicinal products and treatments or improvements thereof.

Patents and exclusivity provisions are granted independently by different authorities. These rights exist in most countries where generic applications for medicinal products are permissible to find a balance between innovations and public health.

1.4.1 Global Institutions responsible for administering the patent system

1.4.1.1 The World Intellectual Property Organization (WIPO)

The WIPO, headquartered in Geneva, was established in 1967 as the successor of the United International Bureaux for the Protection of Intellectual Property (BIRPI), which had been established in 1893 to administer the Berne Convention for the Protection of Literary and Artistic Work and the Paris Convention for the Protection of Industrial Property. The WIPO is one of 17 specialised agencies of the United Nations. Currently, it has 188 member states. It is the global forum for intellectual property services, policy, information and cooperation [14]. WIPO entered into a cooperation agreement with the World Trade Organization (WTO) in 1996.

1.4.1.2 The World Trade Organization (WTO)

The WTO, also based in Geneva, is an intergovernmental organization which regulates international trade. It was created by the Uruguay Round negotiations in Marrakech in 1994 as a successor of the General Agreement on Tariffs and Trade (GATT). There are 161 member states at the time. The function of the WTO is the regulation of international trade and the implementation of WTO trade agreements [15].

1.4.2 TRIPS Agreement

Negotiated at the end of the Uruguay Round negotiation in 1994, where the WTO was established, the Trade Related Aspects of Intellectual Property Rights (TRIPS) introduced intellectual property law into the international trading system for the first time by setting down minimum standards for many forms of intellectual property regulations for WTO member states. It remains the most comprehensive international agreement on IP to date [16].

Among the major requirements of the TRIPS Agreement are the following [17]:

- WTO Member States must provide a minimum level of rights equal to those provided in major global intellectual property treaties by the WIPO, including the Paris Convention on Industrial Property.
- WTO Member States are not allowed to discriminate among the fields of technology in providing patent protection. Before this, many countries did not grant patents for pharmaceutical products.
- Patent protection must be provided for at least 20 years from the date of patent application filing by the WTO Member States.
- The WTO Member States must also provide effective judicial enforcement of IP rights.

1.4.3 Patents

The basic idea of a patent is to encourage inventors to disclose their invention to the public in return for the limited right to exclude others from making or using the invention. A patent is an exclusive right granted by a sovereign state for a certain period of time of at least 20 years for an invention, which is a novel, non-obvious (inventive) and useful (industrial applicable) product or a process or an improvement of those that provides, in general, a new way of doing something, or offers a new technical solution to a problem. Patent protection means that the invention cannot be commercially made, used, distributed, imported or sold by others without the patent owner's consent [18].

There are three technology-based industries where the patent virtually equals the product: the chemical, the biotechnology and the pharmaceutical industry. Unlike in the electronic industry, where patents are often shared among competitors, e.g. by pooling or cross licensing, patents in the pharmaceutical industry are the only effective way to protect and receive a return on the investments necessary for laboratory research and clinical testing before placing a medicinal product on the market. Patent protection for pharmaceutical products is even more important compared to other patent-driven industries because the actual manufacturing process of a pharmaceutical product is often easy to replicate with a fraction of the investment originally needed. In addition, it is possible in many technology-

based industries to keep an invention secret and delay patent-filings until they are put on the market and thereby, to maximize the protection period offered by a patent, whereas the culture of medical research leads to very early disclosure of inventions. This early disclosure results in much shorter periods of patent protection for pharmaceutical manufacturers compared to e.g. manufacturers of consumer electronics [17]. To compensate for the financial loss due to the early disclosure, it is possible in some countries (like the USA and in Europe) to extend the patent protection period (see below).

Beside manufacturing patents there are three different types of patents in the pharmaceutical industry: compound patents, first medical use patents and second medical use patents. Usage patents relate to new indications or modes of administration. Compound patents usually come first, giving patent protection to the compound as such. First use patents are filed if there is evidence for the pharmaceutical relevance of a compound or it has been discovered that it can be used to treat a disease. In case a certain compound and its use in treating a disease are known in the art and it is discovered that it can be used for, e.g. the treatment of another disease or for the treatment of a known indication in a new patient group or with a new dosage form or with a new dosage regimen, a second medical use patent application is filed. It should be noted, that no definition of a new indication exists in the European or US legislation.

1.4.3.1 Patents in the EU

In the EU, patents are granted by the European (EPO) or national patent offices The inventor can choose to apply for a national patent in one or more Member States by filing an application for each state or to submit a single patent application at the EPO based on the European Patent Convention (EPC) for as many out of the 38 contracting Member States as required (European patent). Once the European Patent has been granted, the patent has to be validated in each of the designated states to retain its protective effect and be enforceable against infringers [19]. Thus, it becomes a national right in each Member State and falls under the respective national jurisdiction. This means that a European Patent is a “bundle” of national patents with different periods of validity. Soon, there will be a European patent with unitary effect (“unitary patent”) coming into effect, which will be valid in all 25 participating Member States by filling only one application [20]. The patents are enforced by court proceedings. Measures for the enforcement of intellectual property rights are laid down in Directive 2004/48/EC [21].

To compensate for the long development time and the resulting short patent protection period, due to the early disclosure of new inventions in the pharmaceutical industry mentioned above, which is not sufficient to cover the investment put into research, it is possible to apply for additional protection within the limits of protection conferred by the basic patent by Supplementary Protection Certificates (SPCs). SPCs have been implemented

by Regulation No (EC) 469/2009 (former Regulation No (EEC) 1768/92). Article 13 states that the manufacturer should receive 15 years of patent protection after marketing authorisation of a medicinal product. The certificate *"shall take effect at the end of the lawful term of the basic patent"* but cannot exceed five years from the date it is granted. SPCs have to be applied for at the national patent offices within six months after approval of the marketing authorisation. It is only granted once for the basic patent [22]. According to Article 36 of Regulation No (EC) 1901/2006, an extension of the SPC for additional 6 months is possible if the holder of the marketing authorisation conducted clinical trials in children [23].

The EPC has been in force since 7th of October, 1977. A substantial amendment, the EPC2000, was signed in November 2000. The first relevant stipulation for patenting first medical uses under the old EPC was Article 52(4) [24]:

> *"Methods for treatment of the human or animal body by surgery or therapy and diagnostic methods practised on the human or animal body shall not be regarded as inventions […]. This provision shall not apply to products, in particular substances or compositions,* ***for use in any of these methods****."* (Emphasis added)

The second relevant article for patenting second medical uses under the old EPC1973 was Article 54(5) [25]:

> *"…shall not exclude the patentability of any substance or composition, comprised in the state of the art, for use in a method referred to in Article 52, paragraph 4, provided that its use for any method referred to in that paragraph is not comprised in the state of the art."*

Thus, even though methods for treatment were not patentable, the patentability of first medical use inventions was established by stating that even if the compound was already known in the art, there would still be novelty for first medical uses. The corresponding claim options were available:

> *Compound X for use as an active pharmaceutical substance.*

Or

> *Pharmaceutical composition comprising compound X and, optionally, a pharmaceutical acceptable carrier and/or diluent.*

Second medical use inventions were patentable under the EPC1973 only if they were claimed as a so-called "Swiss-type claim" (process claims):

> *Use of substance/compound X for the preparation of a pharmaceutical composition/manufacture of a medicine for treating or preventing disease Y.*

Article 54(5) of EPC1973 was amended and became Article 54(4) in EPC2000. Additionally, a new paragraph, Article 54(5), was incorporated [26]:

> *"…shall also not exclude the patentability of any substance or composition […]* ***for any specific use in a method*** *[…] provided that such use is not comprised in the state of the art."* (Emphasis added)

Thus, second medical use inventions could be claimed using the so-called EPC2000 (purpose-limited product claims) claim [27]:

> *Compound X for treating disease Y.*

Or

> *Pharmaceutical compositions for treating or preventing disease Y comprising compound X.*

This type of claims confers broader rights than the older Swiss-type claims (G2/08, S. 490 [28]). In decision G2/08 the EPO Enlarged Board of Appeal has held that Swiss-type claims will not be permitted in applications having a filing date on or after 29th January 2011 [28]. Nevertheless, Swiss-type claims and purpose-limited EPC2000 will coexist for many years.

Patent information of the reference medicinal product should not be included in applications for generic marketing authorisations, as they are not part of the evaluation process.

1.4.3.2 Patents in the USA

The patent law of the USA is authorised by the U.S. Constitution. Article 1 Section 8 states [29]:

> *"the Congress shall have power […] To promote the Progress of Science, and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries…"*

The legal basis for patents is the Patent Act. The first Patent Act was enacted by the Congress in 1790. A general revision of the patent laws was enacted in 1952. It is codified under Title 35 of the United States Code [30]. Substantial amendments followed especially within the last 20 years.

The US legal system is a common law system and relies on judicial precedent. Court decisions are a vital part of patent law and litigation by interpreting the constitution and statutes. In some cases, they create law themselves. For example, the "doctrine of equivalents" was first adopted by the US Supreme Court in 1950 and has no independent basis [31].

Patents are granted by the United States Patent and Trademark Office (USPTO). Once issued, the patentee must enforce the patent without help of the USPTO.

Patents granted after 8th of June, 1995 have a 20-year patent life (before 17 years). Similar to Europe, the term of a patent can be extended. Title II of the Drug Price Competition and Patent Term Restoration Act (Hatch-Waxman amendments) enacted in 1984, extended the patent life so that patent holders whose patents claim a human drug product could recoup for lost marketing time while developing a product and awaiting FDA's approval (35 USC § 156). The regulations governing the Patent Term Restoration program are codified in 21 CFR 60 [32]. A maximum of 5 years can be restored to the patent but the total patent life for the product cannot exceed 14 years after approval of the marketing application. The patent is eligible for extension if the basic patent has not expired. The extension application has to be submitted within 60 days after approval. The extension is only granted once. Nevertheless, a further extension of 6 months is possible for a paediatric indication [33, 34].

Medical use claims for new uses of previously known pharmaceutical compounds are patentable under U.S. law. But unlike in Europe, there is no discrimination between first and second medical use patent claims. Instead of the second medical use formats mentioned in section 1.4.3.1, the proper U.S. format relates to "methods of treatment" of the new use [35]:

> *A method of treating a patient suffering from a disease Y by administering an effective amount of compound X to the patient.*

The legal basis can be found in 35 USC § 101, which states [36]:

> *"Whoever invents or discovers any new und useful process, machine, manufacture, or composition of matter,* ***or any new and useful improvement thereof****, may obtain a patent therefor, subject to the conditions and requirements of this title." [Emphasis added]*

A "process" is defined in 35 USC § 100(b) [37]:

"The term "process" means process, art or method, and includes ***a new use of a known*** *process, machine, manufacture, composition of matter, or material." [Emphasis added]*

Second medical use patent protection is available for a new use of a known compound, a new use of a known compound that was not successful for its initial purpose, or for a new use of a known compound previously discovered for non-medical uses. A new dosage regimen of a known drug to treat a known illness might be patentable under US law, depending on the available support for non-obviousness [35]. For changes of a previously approved drug concerning a new indication, dosage form, strength, route of administration or an API change (different salt, ester, enantiomer etc.) a NDA application under Section 505(b)(2) of the FD&C Act has to be filed. The regulation governing this application are codified in 21 CFR 314.54 [38]. This type of application is a NDA with full reports of safety and effectiveness but not all data have been developed by the applicant. Section

505(b)(2) was also added to the FD&C Act by the Hatch-Waxman Amendments. It permits approval of applications other than those for duplicate products, i.e. generics [39]. The underlying idea is to encourage innovation without creating duplicate work and studies.

Whereas patent information is not part of the marketing authorisation process in Europe, the FDA reviews the patent protection situation of the reference listed drug. A generic applicant must include in its ANDA a patent certification to each patent which claims the reference listed drug or its use published in the Orange Book (Approved Drug products with Therapeutic Equivalence Evaluations) by the FDA for which the applicant is seeking approval. There are four different types of certification (CFR 314.94(a)(12)(i)(A)(4), [9]):

- Paragraph I certification: the applicant certifies that the NDA holder submitted no patent to the FDA. The FDA can approve the ANDA once assessment process is finished.
- Paragraph II certification: the applicant certifies that the patent has expired. The FDA can approve the ANDA once assessment process is finished.
- Paragraph III certification: the applicant states the date on which the patent will expire. The FDA can approve the ANDA as soon as the patent has expired and the assessment process is finished.
- Paragraph IV certification: the applicant certifies that the patent is invalid, unenforceable or will not be infringed by the manufacture, use or sale of the drug product for which the ANDA is submitted.

By a paragraph IV certification, the generic manufacturer challenges the patent and constitutes an act of infringement. After receipt of a letter of acceptance from the FDA that the ANDA filing has been accepted, the ANDA applicant has to notify the patent and the NDA holder about the paragraph IV certification within 20 days. If the patent holder files an infringement suit against the generic applicant within 45 days of the paragraph IV certification, the approval to market the generic medicinal product is automatically stayed for 30 months, unless, before that time, the patent expires or is judged to be invalid or not infringed [40, 41]. The FDA provides tentative approval of the generic [42]:

> *"If a generic drug product is ready for approval before the expiration of any patents or exclusivities accorded to the reference listed drug product, FDA issues a tentative approval letter to the applicant. […] FDA delays final approval of the generic drug product until all patent or exclusivity issues have been resolved. A tentative approval does not allow the applicant to market the generic drug product."*

If the patent holder does not file an infringement suit, the FDA can approve the generic medicinal product once assessment of the ANDA is completed.

For reference listed drugs covered only by method of use patents, another way of achieving an ANDA approval exists: the filing of a so-called “Section viii” certification together with the use of a skinny label. The legal basis from which Section viii certifications derive their name, 21 USC §355(j)(2)(A)(viii) states [43]:

> *“if with respect to the listed drug […] information was filed [by the innovator company] […] for a method of use patent which does not claim a use for which the [ANDA] applicant is seeking approval under this subsection, [the ANDA shall contain] a statement that the method of use patent does not claim such a use.”*

So, if the ANDA applicant submits a statement to the FDA that it will not market its generic medicinal product for any use covered by the patents listed in the Orange Book, he/she may seek approval under Section viii. The proposed skinny label for the generic must also remove all references to the method of use patent(s).

However, the FDA, denying sufficient knowledge of patent law to analyse the content and scope of the patents listed in the Orange book, requires each NDA holder to supply a “use code”. This code is intended to serve as a short description of the scope of each method of use patent in the Orange Book. The FDA relies on these codes to identify which indications are patent protected and must be removed from the generic product information.

Unlike a Paragraph IV certification, a Section viii certification does not lead to a stay of a final approval and the NDA holder does not have to be informed about its filing.

1.4.4 Roche-Bolar Exemption

The Roche-Bolar exemption, also called in the USA the Hatch-Waxman exemption or safe harbour exemption, is an exemption to the rights conferred by patents on medicinal products which allows research and tests for preparing generic marketing authorisation applications.

In the USA, the exemption was included into patent law after the Roche-Bolar court case by the “Hatch-Waxman Act” (Drug Price Competition and Patent Term Restoration Act) in 1984, Section 271(e) [44]:

> *“(1) It shall not be an act of infringement to make, use, offer to sell, or sell within the United States or import to the United States a patented invention […] solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs […].*
>
> *(2) It shall be an act of infringement to submit –*
>
> *(A) an application under section 505(j) of the Federal Food, Drug, and Cosmetic Act […] for a drug claimed in a patent or the use of which is claimed in a patent, […]*

if the purpose of such submission is to obtain approval under such Act to engage in the commercial manufacture, use, or sale of a drug, […] claimed in a patent or the use of which is claimed in a patent before the expiration of such patent."

In Europe, Article 10 (6) of Directive 2004/27/EC [45] amending Directive 2001/83/EC introduced the Roche-Bolar exemption into European patent law:

"Conducting the necessary studies and trials with a view to the application of paragraphs 1, 2, 3 and 4 [of Article 10 of Directive 2001/83/EC] and the consequential practical requirements shall not be regarded as contrary to patent rights or to supplementary protection certificates for medicinal products."

This exemption from patent infringement is the key for generic manufacturers to produce and apply for approval of generics in advance of the patent expiration and to market of these medicinal products without delay once the innovator product is not protected by patent or exclusivity rights anymore.

1.4.5 Exclusivity provisions

In addition to patent rights, the EMA and the FDA have implemented various provisions to extend the period during which innovator companies can market their medicinal products free of generic competition to incentivize ongoing research and innovation. In case patent protection for the medicinal product has expired, these exclusivity provisions might be the only protection for the innovator manufacturer.

There are two different types of exclusivity provisions: data exclusivity and market exclusivity. Data exclusivity means that within a limited time-period the pre-clinical and clinical data obtained for the marketing approval of the innovator's product may not be referenced in marketing authorisation applications of a generic company. Thus, generic applications for marketing authorisations cannot be submitted. During the period of market exclusivity, generic applications can rely on the innovator's data and hence can be filed but cannot be approved by the authorities.

1.4.5.1 European Union

In the EU, innovator companies benefit up to eleven years (8+2+1) of exclusivity for new medicinal products. For marketing authorisations applications filed before November 2005 the period of data exclusivity varies from Member State to Member State and is either 6 or 10 years from the date of the first authorisation in Europe (Directive 2001/83/EC not amended, Article 10(1)(a)(iii) [46]). For marketing authorisations applications filed after November 2005 the period of data exclusivity is harmonised by Directive 2004/27/EC in 2004 as 8 years, which is followed by an additional 2-year period of market exclusivity. This period of market exclusivity can be extended by an additional year if the initial holder

of the marketing authorisation obtains an authorisation for at least one new therapeutic indication with significant clinical benefit within the first eight years of data exclusivity [45].

For orphan medicinal products, i.e. a medicinal product to diagnose, prevent or treat a life-threatening or very serious condition afflicting no more than five in 10,000 people in the EU, a 10-year period of market exclusivity is granted. During this period, neither an application for a marketing authorisation will be accepted nor will a marketing authorisation be granted or extended. This period may be extended to 12 years for paediatric products or reduced to 6 six years if, at the end of the fifth year, the criteria for an orphan medicinal product are no longer met [23, 47].

1.4.5.2 USA

The Drug Competition and Patent Term Restoration Act (Hatch-Waxman Amendments) provides up to 5 years market exclusivity for a new chemical entity (NCE) from the date of approval. During this period the FDA cannot approve or even accept a 505(b)(2) application or an ANDA for a medicinal product that contains the same active moiety. However, a 505(b)(2) application or abbreviated application may be submitted if a Paragraph IV Certification is included. For significant innovations (e.g. a new indication) supported by post-approval clinical study reports on a previously approved medicinal product, a market exclusivity of 3 years is granted (21 CFR 314.108 [48]).

For orphan medicinal products, i.e. a medicinal product intended to treat diseases and conditions that affect less than 200,000 Americans, a 7-year period of market exclusivity is provided (21 CFR 316.31 [49]).

If the FDA requests certain paediatric studies prior to the clinical trials, a 6-months extension to existing patent or exclusivity rights (after all other forms of exclusivity have expired) can be obtained [50].

Since the decisions in Mova Pharmaceuticals, Inc v. Shalala in 1998, the first generic company to submit a complete ANDA containing a Paragraph IV certification to a listed patent receives market exclusivity for 180 days (21 USC § 355(B)(iv) [40, 43]). The FDA published further guidance for the case that one [51] or more [52] abbreviated applications for the same medicinal product are submitted on the same day. In the latter case, the exclusivity period is shared among the generic applicants. This 180-day period of market exclusivity provides a strong financial incentive for a generic manufacturer since the price of a generic medicinal product decreases significantly once more generic competitors for the same innovator medicine enter the market.

1.5 Generic substitution

Usually, the doctor prescribes a medicinal product which the patient gets at the pharmacy. Sometimes a pharmacist is required to substitute a different medicinal product than the one prescribed.

Therapeutic substitution is a form of substituting one medicinal product for another. It occurs if a pharmacist substitutes a chemically different medicinal product which belongs to the same pharmacologic class or to the same therapeutic class for the medicinal product the physician actually prescribed. Generic substitution is absolutely different form therapeutic substitution. Here, a generic medicinal product is substituted for a branded medicinal product. However, both have the same active substance and the same dosage form and strength.

Many governments have introduced generic substitution to increase the use of generic medicines and to reduce costs. It is allowed in fourteen European countries (in 2011), but the characteristics of the policy can differ from country to country. In six European countries (Finland, France, Germany, Norway, Spain and Sweden) generic substitution is mandatory but only optional in the others (Czech Republic, Denmark, Hungary, Italy, Latvia, The Netherlands, Poland and Portugal) [53]. Because the review of the regulations of all European Countries would go beyond the scope of this thesis, only the regulations in Germany will be discussed in detail and compared to the regulations in the USA.

1.5.1 Generic substitution in Germany

In 2013, generic medicinal products accounted for 75 % of the volume of pharmaceuticals covered by basic health coverage in Germany [54]. The use of generic medicines here is mainly driven by physician budgets and incentives for physicians prescribing generics. Also prescribing by International Nonproprietary Name (INN) is encouraged, which further allows the pharmacist to dispense a generic medicinal product.

The conditions for substitution of a medicinal product for a cheaper one containing the same active substance is governed by Section 129 of Volume V of the Social Insurance Code (Fünftes Sozialgesetzbuch – SGB V, [55]). The so-called “aut-idem-Regulation” was implemented first in 2002 by the Pharmaceutical Expenditure Limitation Act (Arzneimittelausgabenbegrenzungsgesetz – AABG). Generic substitution is compulsory and only prohibited if it is excluded by the physician on the prescription or if the medicinal product is on a negative list (Substitutionsausschlussliste) issued by the Federal Joint Committee (Gemeinsamer Bundesausschuss – G-BA). This list contains mainly medicinal products with a narrow therapeutic index [60]. A medicinal product can be substituted if it is identical in active substance, potency and package size and has the same or an interchangeable dosage form. Interchangeable dosage forms are defined in Attachment VII of the “Me-

dicinal Products Directive" (Arzneimittelrichtlinie) [56]. Interestingly, a medicinal product can be substituted even if not all of the indications match, i.e. the other medicinal product has to be approved for only one corresponding indication to be eligible for substitution. This means that an innovator medicinal product with one or more patent protected indications can be and is obliged to be substituted as soon as there is a generic version available which is approved for at least one not protected indication. The pharmacist has to substitute for one of the three cheapest eligible medicinal products unless the statutory health insurance has a rebate agreement with a certain manufacturer. In this case, the pharmacist has to substitute a medicinal product from this manufacturer.

1.5.2 Generic substitution in the USA

In 2013, the use of generics was 86 % of all dispensed prescriptions within the off-patent (unprotected) market in the USA [57].

Generic substitution laws are determined by the individual states. All states have adopted laws concerning generic substitution but they vary in several important ways. In 15 states generic substitution by the pharmacist is mandatory unless the physician specifies that the branded medicinal product should be dispensed as written. The other states adopted a more permissive substitution law, where the pharmacist is allowed but not required to substitute a generic medicinal product as long as the physician did not state otherwise. In some states the pharmacist must also get consent from the patient before substitution [58]. For people enrolled in Medicaid, the largest social health care program for families and other people with low income in the USA, generic substitution is mandatory in 40 states [59]. All state laws generally require either that the substitution is limited to medicinal products on a specific list (positive formulary approach) or is prohibited for medicinal products on a specific list (negative formulary approach).

Most states have adopted the FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (Orange Book) as the legal basis for substitution of generic products. However, the FDA does not regulate generic substitution nor does it dictate which medicinal product may be substituted for another. Generic substitution is done by the physician or the pharmacist, depending on states' law. The Orange Book serves as a guide for identifying suitable generic alternatives for an innovator medicinal product. It was first published in 1979 to assist states and facilitate generic substitution. By the Hatch-Waxman Amendments in 1984, sections concerning patents and market exclusivity regarding reference listed drugs were introduced. The Orange Book lists all products that have been approved by the FDA for safety and effectiveness, alphabetically by the ingredients in the product. It also lists a therapeutic equivalence code for all products, "A" codes and "B" codes (first letter), together with additional information (second letter):

*"A Drug products that FDA considers to be **therapeutically equivalent** to other pharmaceutically equivalent products, i.e., drug products for which:*

(1) there are no known or suspected bioequivalence problems. These are designated AA, AN, AO, AP, or AT, depending on their dosage form; or
(2) actual or potential bioequivalence problems have been resolved with adequate in vivo and/or in vitro evidence supporting bioequivalence. These are designated AB.

B Drug products that FDA at this time, considers NOT to be therapeutically equivalent to other pharmaceutically equivalent products, i.e.,

Drug products for which actual or potential bioequivalence problems have not been resolved by adequate evidence of bioequivalence. Often the problem is with specific dosage forms rather than with the active ingredients. These are designated BC, BD, BE, BN, BP, BR, BS, BT, BX, or B"* [60]

Therapeutical equivalents are medicinal products that are pharmaceutical equivalents which are expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labelling [60].

1.6 Product information

The product information for human medicines includes documents like the summary of product characteristics, labelling and package leaflet. They are a key part of the marketing authorisation of medicinal products and included in every application, because all product information has to be approved by the competent authorities. In the USA, the term "Labeling" refers to the entire product information, whereas in Europe "Labelling" refers to the outer packaging only. In the context of this thesis "Labelling" refers to the complete product information as well. In Europe, labelling indicates the information on the outer packaging, as mentioned, and the summary of the product characteristics [SmPC] provides all information for healthcare professionals, while the package leaflet is the basis for patient information. Labelling requirements are based on Article 54 to 57 of Directive 2001/83/EC. Articles 58 and 59 of this Directive are the legal basis for the package leaflet [1]. Article 59 states:

"The package leaflet shall be drawn up in accordance with the summary of the product characteristics…"

The SmPC is described in the next section.

1.6.1 SmPC requirements in the European Union (EU)

Article 8(1) of Directive 2001/83/EC [1] states

"In order to obtain an authorization to place a medicinal product on the market […] an application shall be made to the competent authority of the Member State concerned."

Article 8(3) of this Directive [1] describes the content of the application:

"The application shall be accompanied by the following particulars and documents, […]

(j) A summary, in accordance with Article 11, of the product characteristics, […]."

In general, the Summary of Product Characteristics (SmPC) summarizes the chemical, pharmaceutical, pharmacological and hazardous properties of a medicinal product as well as its use as agreed between the pharmaceutical company and the competent authority. It provides the basic information for healthcare professionals on how to use the medicinal product safely and effectively. Since the SmPC is part of the marketing authorisation application, it can only be changed after approval via a variation procedure. The European Medicines Agency (EMA) published "*A guideline on Summary of Product Characteristics (SmPC)*" for further assistance [61].

As mentioned above, the SmPC has to be in accordance with Article 11 of Directive 2001/83/EC [1]. Herein, the content of the SmPC is described. Concerning the SmPC of generics, which in general, must contain the same information as that of the SmPC of the reference medicinal product, information can only be found in the last paragraph of Article 11:

"For authorisations under Article 10, those parts of the summary of product characteristics of the reference medicinal product ***referring to indications or dosage forms which were still covered by patent law*** *at the time when a generic medicine was marketed* ***need not be included.****"* [Emphasis added]

Article 3(3)(b) of Regulation (EC) No 726/2004 [2] gives only little more advice:

"the summary of the product characteristics ***is in all relevant respects consistent with that of the medicinal product authorised*** *by the Community* ***except*** *for those parts of the summary of product characteristics* ***referring to indications or dosage forms which were still covered by patent law*** *at the time when the generic medicine was marketed;"* [Emphasis added]

The EMA guideline on SmPCs mentioned above [61] does not contain any information regarding SmPCs of generic medicinal products at all (for patents please see section 1.4.3). However, little guidance can be found on the EMA website for generic medicinal products authorised via the CP or on the Head of Medicines Agencies (HMA) website for generic medicinal products authorised via DCP or MRP in the Question and Answers section, respectively. The EMA web page describes as follows (Questions and answers on generic and hybrid applications [62]): As mentioned above, the patent situation may differ in the different Member States since it is the patent holder's decision where to apply for a

patent. How this will be reflected in the product information is answered in Q&A no. 16. It is not possible to have different product information for a particular medicinal product authorised via the centralised procedure. However, to take account of different patent situations in the various Member States, it is possible to submit duplicate applications which contain fewer indications (or pharmaceutical forms) than the original marketing authorisations when this is required to market the medicinal product in Member States where a specific indication (or pharmaceutical form) is patent protected [63]. As soon as the relevant patents expire the SmPC has to be harmonised by extending the indications or pharmaceutical forms [62]. Q&A no. 17 answers the question which sections of the SmPC can be deleted in connection with a patent protected indication [63]. Directly related information can be deleted from sections 4.1 (therapeutic indications), 4.2 (posology and method administration) and 5.1 (pharmacodynamics properties) of the SmPC. Safety-related information in sections 4.3 to 4.8 (4.3 Contraindications, 4.4 Special warnings and precautions for use, 4.5 Interaction with other medicinal products and other forms of interaction, 4.6 Fertility, pregnancy and lactation, 4.7 Effects on ability to drive and use machines, 4.8 Undesirable effects) should be maintained for public-health reasons. Any other deletions will need to be properly justified and discussed with the Member States concerned.

The Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human issued a Question & Answers Document regarding usage patents in October 2012 [64]. Notwithstanding from the information given on the EMA web page, Question 2 referring to deleting further patent-connected sentences in other sections, e.g. in posology, contraindications or warnings is answered as follows:

> *"The Directive states only the exclusion of information referring to indication and dosage forms. Any other deletion connected to the patented indications or dosage forms must be properly justified and discussed with the member state concerned."*

As a standard statement to explain patients why therapeutic indication(s) or dosage form(s) may be lacking in the package leaflet is explained in Question 3, that including such a statement is a national decision of Member States. If a Member State requests this information, the following sentence should be included, using the 'blue box concept':

> *"(Active substance) which is contained in (product) (may also be/is also)* authorised to treat other conditions which are not mentioned in this leaflet. Ask your doctor or pharmacist if you have further questions. * (as appropriate for the national market)"*

Questions 4 and 5 refer to the SmPC. Question 4 states that the SmPC of the reference medicinal product or of the European reference medicinal product is the basis for evalua-

tion and recognition. No information due to a usage patent will be deleted in the final product information (SmPC, package leaflet and labelling) as

> *"[t]he patent situation in the different Member States concerned by the application do not have an impact during the MRP/DCP itself as this is out of the scope for competent authorities […]."*

The Member States will recognise the final SmPC, PIL and labelling including all indications and dosage forms. It is up to the applicant to inform the authorities of the modifications needed to the final national product information taking into account the patent situation. As soon as the patent expires the marketing authorisations holder must contact the national competent authority and apply for revised product information [64].

1.6.2 Labeling requirements in the USA

For marketing authorisations of medicinal products in the USA a document like the Summary of Product Characteristics as in Europe does not exist. But of course rules and regulations concerning labelling of medicinal products are available as well. While Section 21 CFR 201 "*Labeling*" [65] of the CFR contains all regulations concerning the labelling of medicinal products, especially Section 21 CFR 201.56 "*Requirements on content and format of labeling for human prescription drug and biological products*" and Section 21 CFR 201.57 with special requirements, information concerning the labelling of generic drug products can be found in Section 21 CFR 314 Subpart C "Abbreviated Applications". 21 CFR 314.94(a)(8)(iv) "*Comparison of approved and proposed labeling*" states:

> *"A side-by-side comparison of the applicant's proposed labeling including, if applicable, any Medication Guide required under part 208 of this chapter with the approved labeling for the reference listed drug with all differences annotated and explained.* ***Labeling*** *(including the container label, package insert, and, if applicable, Medication Guide)* ***proposed for the drug product must be the same as the labeling approved for the reference listed drug****, except for changes required because of differences approved under a petition filed under 314.93 or because the drug product and the reference listed drug are produced or distributed by different manufacturers. Such differences between the applicant's proposed labeling and labeling approved for the reference listed drug may include […] or* ***omission of an indication or other aspect of labeling protected by patent*** *accorded exclusivity under section 505(j)(5)(F) of the act."* (Emphasis added)

A Reference Listed Drug (RLD) is defined as [66]

> *"an approved drug product to which new generic versions are compared to show that they are bioequivalent. A drug company seeking approval to market a generic equivalent must refer to*

> *the Reference Listed Drug in its Abbreviated New Drug Application (ANDA). By designating a single reference listed drug as the standard to which all generic versions must be shown to be bioequivalent, FDA hopes to avoid possible significant variations among generic drugs and their brand name counterparts."*

Section 21 CFR 314.93(b) mentioned above allows differences only in route of administration, dosage form, strength or where one active ingredient is substituted for another [67].

But here, like in Europe, real guidance on how the labelling has to be done in case of a patent protected indication for example is missing as well. Even in the "*Guidance for Industry: ANDA Submissions – Content and Format of Abbreviated New Drug Applications*" only one sentence in this context can be found:

> *"Applicants should also submit an exclusivity statement regarding their marketing intentions. This is relevant* ***when the generic applicant intends to remove or carve out any protected indication(s) from the labeling*** *in order to gain market entry prior to a use's expiry."* [Emphasis added]

This exclusivity statement, the so-called "Section viii" certification is explained in section 1.4.3.2.

2. Issues arising from the current situation

Even though regulatory legislation and procedures differ significantly in the EU and the USA, the current situation concerning skinny labelling and second medical use claims is the same. It is an area of conflict for all stakeholders because of opposing interests and a lack of legislation/guidance by the authorities.

2.1 Health authorities/statutory health insurances

In 2013, health expenditures were 314.9 billion Euro in Germany almost double that of 1992 (1992: 158.9 billion €) and 2.9 trillion Dollar in the USA, four times more than 1990 (1990: 724.3 billion $) [68, 69]. To curb the continuously increasing costs in the health care systems, there is a need for safe and efficacious medicinal products at low prices on one hand. In Germany, a generic medicinal product costs at least 66 % less than the brand name product [70], in the US, 80 to 85 % [71]. On the other hand, continuous research and development of new medicinal products or new uses for known medicines is wanted to satisfy so far unmet medical needs and thereby improving public health.

2.2 Innovator companies

The innovative improvement of known substances gives a chance for significant therapeutic progress while reducing the effort and the risk for the company. The market relevance can be immense, even if the active substance and first use have been known for many years. Second medical uses also have an advantage for the patients because safety profile and side effects of the compounds are already known. This is also acknowledged by the legislator by second medical use claims being patentable. But the time and money needed for the clinical development of a new indication for a known medicine does not differ significantly from that for a new substance, due to the regulatory requirements [72]. And even if the innovator company finds a new indication for the known substance and receives approval to market the product with the new characteristics, this medicinal product can be substituted any time as soon as there is an approved generic medicinal product containing the same active substance available, because generic substitution is mandatory in many countries. Thus, the generic product has access to new markets without any costs and the innovator company has no opportunities to refinance its investments. In the USA, this is especially relevant for generic medicinal products approved by a Section viii certification. These medicinal products, which are considered therapeutically equivalent to the RLD, are often prescribed for all uses for which the RLD is approved, including the patent protected ones.

This problem is even more pronounced in all countries, if the prescription is by INN. Since there is no indication on the prescription, the pharmacist will dispense the cheapest me-

dicinal product available and it is almost inevitable that a generic medicine will be routinely (and automatically) used for a patent protected indication.

Tenders for rebate agreements issued by statutory health insurance companies are won by the manufacturer who offers the medicinal product at the lowest price. Patent protection of certain indications is not considered. The innovator company has no opportunity to prevent a generic medicinal product, which will almost certainly win the tender, from being used for a patent protected indication.

Furthermore, second medical use claims are difficult to enforce with regard to cross label use and skinny labelling. Cross label use means the use of a medicinal product for an approved and patented indication that is not mentioned in the product information, i.e. SmPC and PIL. In contrast, “off label use” is the use of a medicinal product for a non-approved indication. But both terms are used synonymously.

2.3 Generic companies

European and US regulatory legislation is drafted to facilitate market access of generic medicinal products, e.g. by abridged/abbreviated marketing authorisation applications without costly preclinical studies and clinical trials. By introduction of the Roche-Bolar-exemption and carve-outs of patent protected indications in the product information of generic medicinal products (skinny label), market entry of generics becomes possible as soon as the first period of patent protection/exclusivity of an innovator medicinal product expires. Of course, the generic manufacturer is interested in a maximum market share for its product. However, because real regulatory legislation/guidance for handling second medical use claims does not exist and due to mandatory generic substitution laws the generic industry has to deal with an uncertain legal situation (for actual jurisprudence see section 3).

A generic company has no influence on the substitution of its medicinal product for a patent protected indication. In Germany, as mentioned, a medicinal product with the same active substance will be substituted as long as one indication matches and the other obligations are fulfilled [73]. This poses the risk that the generic company can be sued for direct/indirect infringement, even if the patent protected indication has been carved-out and the medicinal product is authorised only for the off-patent indication.

Tenders for rebate agreements are by active substance not by indication. It is not possible for a generic company to apply for a tender only for non-protected indications.

2.4 Physicians

Freedom in prescribing and treating is a principle in medical treatment to ensure that a physician has the free choice of treatment because of his expertise. But this freedom is

curtailed more and more by budget limitations and managed care models. Health authorities state that the doctors should not only be committed to patient well-being but also have an obligation to prescribe inexpensively. Physicians are encouraged to prescribe generic medicinal products or by INN – and have to – if they want to stay within their budgets. They also get financial incentives for doing so. Nevertheless, prescribing a generic medicinal product for a carved-out indication infringes the patent and the physician creates the nexus between the medicinal product as such and the protected use. But in almost all cases the prescribing physician does not know what indications are approved for a generic medicine. And no sensible innovator company would pursue the prescribing physicians. Hence, there is no case law on this matter.

2.5 Pharmacists

Like the physician, the pharmacist is obliged to limit health care costs. The substitution law described above constrains the pharmacist to substitute a generic medicine if not excluded explicitly by the prescribing doctor or the health authority. Since there is no indication written on the prescription, which often contains only the INN, the pharmacist generally does not know if he has dispensed a generic for a patent-protected indication. In Germany, the pharmacist has to substitute as long as the criteria of § 129 SGB V are fulfilled: the medicinal product has to be the same in active substance, potency, and needs to have the same or an interchangeable dosage form, identical package size (in which a N3 package containing 100 tablets can be substituted by a N3 package containing only 60 tablets, as long as N3 is printed on both of them) and is authorised for at least one matching indication. The latter has not been changed even though the Higher Regional Courts (Oberlandesgerichte) of Hamburg (02 July 2009, 3 U 221/08 [74]) and Frankfurt (11 March 2010, 6 U 198/09 [75]) came to a contrary decision. In Germany, the pharmacist can reject the substitution since 2008 if he claims pharmaceutical concerns. But as this has to be justified and the pharmacist faces the risk of not getting reimbursed, rejection of substitution by the pharmacist happens only in very few cases [76]. Many countries provide incentives to pharmacists for dispensing a generic medicinal product. In the UK, for example, the pharmacist gets reimbursed by the National Health Service (NHS) the same amount for a generic as for a branded medicinal product, if the prescription is by INN, so the profit margin is higher for dispensing a generic. Like prescribing, dispensing a medicinal product for a carved-out indication infringes a patent as well. Here, the same is true as said for the physicians, usually the pharmacist does not know all the indications the generic medicinal product is approved for and moreover, does not know which indication it is prescribed for. Therefore no innovator company has pursued a dispensing pharmacist yet.

2.6 Patients

Naturally, the patient is interested in cheap medicines and low co-payment. Prescription by INN, as it is encouraged in Germany and very common in other countries like the UK, mandatory or incentivised generic substitution and prescriptions containing no indication lead to almost inevitable dispensing of generic medicinal products through the pharmacy. The substituted medicinal product can vary depending on the actual price of the cheapest medicinal products (cheapest three in Germany) containing the respective active substance or on the actual manufacturer who won the tender for the rebate agreement of the respective health insurance company. So, neither the doctor nor the patient really knows which medicinal product the patient actually will receive at the pharmacy. The medicinal products can have different characteristics, like size, shape, colour, and formulation, even though they contain the same active substance and are “substantially the same” or pharmaceutic/therapeutic equivalents. In Germany the meaning of “interchangeable dosage form” is very broad [56]. And even worse, if a generic medicinal product with a “skinny label” is substituted where the indication and/or posology for this indication is missing in the PIL for which it was actually prescribed, the patient might start to be sceptical whether the physician has prescribed the right medicine. This could lead to declining confidence in the doctor’s expertise, noncompliance and discontinuation of therapy and worsening of the disease or condition. Obviously, this does not contribute to reducing health care costs.

3. Actual Jurisprudence

> *"The patent shall have the effect that the proprietor of the patent alone shall be entitled to use the patented invention within the scope of the law in force."* (German Patent Act, Section 9 [77]).

Patents are granted nationally, so that infringement is only possible in a country where a patent is in force. Patent infringement can be direct or indirect, the latter is also called contributory in some countries. The wording defining direct patent infringement varies in the legislation of the different countries, but in general is defined as producing, offering, putting on the market (selling or offering to sell) or using a product or process or importing or possessing such a product or process which is protected by a patent without the consent of the proprietor (e.g. German Patent Act Section 9 [77], United Kingdom: Patents Act 1977 Section 60(1) [78], The Netherlands: Patent Act 1995 Article 53 [79], USA: 35 USC § 271 [80]). Consent is typically by granting a license. Indirect infringement is defined as supplying or offering to supply (in the United States also selling or offering to sell) means relating to an essential element or part of the invention while the patent is in force and without consent of the proprietor if the person knows or if it is evident that those means are suitable and intended for using that invention (German Patent Act Section 10 [77], UK Patents Act 1977 Section 60(2) [78], NL Patent Act 1995 Article 73 [79], 35 USC §271 [80]). The US law also includes "induced infringement" (35 USC §271(b) [80]):

> *"Whoever actively induces infringement of a patent shall be liable as an infringer."*

If the infringing act is done in private and for non-commercial purpose there is no infringement – neither direct nor indirect.

Surprisingly, even though second medical use claims have been granted by the EPO since the 1980s (and – as method of treatments claims of the new use- much longer in the USA), there have been only a few cases upon infringement of such claims. It has to be noted, that there have been no cases regarding EPC2000 claims yet. The following sections give a non-exhaustive overview of landmark decisions in Germany, UK, the Netherlands and in the US.

3.1 Germany

The "Benzolsulfonylharnstoff" (BGH, 20 January 1977, X ZB 13/75 [81]) and "Arzneimittelgebrauchsmuster" (BGH, 05 October 2005, X ZB 7/03 [82]) decisions suggested that in order to infringe a second medical use claim, a product has to be "manifestly arranged" ("sinnfällig hergerichtet") for the claimed use. This means the product will only (directly) infringe if it is manifestly arranged in a way to be used in the claimed indication or if the label includes said claimed indication [83]. There are some well established cases in

Germany concerning infringement of second medical use claims. The first three follow the BGH judgment.

3.1.1 "Ribavirin" – District Court (Landgericht) Düsseldorf, 24 February 2004, 4a O 12/03 [84]

The plaintiff is proprietor of the European Patent EP 0 903 148 B1 (the '148 patent) which was granted in Germany on 10 October 2001. The patent claims a "*combination therapy for eradicating detectable HCV-RNA in patients having chronic hepatitis C infection*".

The '148 patent has Swiss-type claims relating to the use of ribavirin for the treatment of HCV infections as follows:

Claim 1:

1. *The use of ribavirin for the manufacture of a pharmaceutical composition for treating a patient having chronic hepatitis C infection to eradicate detectable HCV-RNA*
2. *by a method comprising administering an effective amount of ribavirin in association with an effective amount of interferon alpha*
3. *for a time period of 40 – 50 weeks*
4. *wherein the patient is one having failed to respond to a previous course of interferon alpha therapy, characterised in that*
5. *the patient has a viral load of greater than 2 million copies per ml of serum as measured by RNA quantitative PCR*
6. *of a HCV genotype 1 infection.*

Claim 10:

> *The use as claimed […] wherein the amount of ribavirin administered is 400 – 1200 mg per day, preferably 800 – 1200 mg per day […].*

The defendant produces ribavirin capsules containing 200 mg ribavirin, Ribavirin Meduna, on behalf of another company. There is no marketing authorisation for ribavirin in Germany but inter alia in Georgia.

The plaintiff claimed that the contested embodiment infringed its '148 patent. As proof of direct infringement the package insert (PIL) was presented. In the section "Indications" is stated [84]:

> "*For the treatment of patients with chronic Hepatitis C who have not responded to treatment with alpha-interferon on account of a contra-indication or intolerance. As an accompanying therapy for patients with chronic Hepatitis C who are being treated with alpha-interferon.*"

In the section "Dose to be administered is stated:

> "*Patients with Hepatitis C:*

Approx. 15 mg/kg.i.e. (800-) 1200 mg Ribavirin Meduna per day are recommended […]. Ribavirin Meduna on its own does not eliminate HCV. If Ribavirin Meduna capsules are applied as an accompanying therapy with interferon treatment, […]. (24-) 48 weeks are recommended."

In the section "Prescription" is stated:

"*The preparation is designed for treatment of Lassa Fever, haemorrhagic Fever, Hepatitis C infections (HCV). The preparation is designed for using against Hepatitis C in patients who previously did not use Alpha-Interferon due to any causes […] or who suffer from non-endurance of Alpha-Interferon. As a concomitant therapy with Alpha-Interferon in the patients suffering from chronic Hepatitis C.*"

The Court did not follow this claim and held that even though it was mentioned in the package leaflet that ribavirin could be co-administered with alpha-interferon, the main use intended was ribavirin monotherapy. Furthermore, there was no specific reference in the PIL to the specific patient group (with a certain virus load in the serum and a HCV genotype 1 infection). The ribavirin product was therefore not manifestly arranged for the intended use of the patent. Not even the submitted evidence that the medicinal product was available in pharmacies in Germany and that more than 50 % of the Hepatitis C patients belong to the patient subgroup claimed in the patent in suit could persuade the court. Although the court noted that it could not exclude that patients belonging to this special subgroup described in the '148 patent are treated with the contested embodiment it dismissed the claim on infringement.

3.1.2 "Cistus Incanus" – Düsseldorf Court of Appeal, 31 January 2013, 2 U 54/11 [85]

The defendant-respondent is proprietor of the European Patent EP 1 837 029 B1 (the '029 patent) which was granted in Germany on 8 October 2008. The patent claims a "*Composition for prevention and treatment of coughs and colds*".

The '029 patent contained Swiss-type claims relating to the use of Cistus incanus for the prophylaxis and/or treatment of colds caused by rhinoviruses. After opposition proceedings claims 1 und 2 of the '029 patent were amended and read as follows:

Claim 1:

1. *The use of Cistus for producing a composition*
2. *having an antiviral activity directed against rhinoviruses*
3. *for reduction of the infectiousness of rhinoviruses*
4. *for the prevention of common cold diseases*

5. *wherein the common cold disease comprises a primary infection, caused by rhinoviruses.*

Claim 2:

The use as claimed in claim 1 wherein the plant is chosen from Cistus incanus.

The plaintiff-appellant manufactures Cistus incanus capsules, sprays and teas and sells them through a networking management system with more than 300,000 independent distributors. One of these distributors sent an email on 29 April 2009 in which the use of Cistus incanus for the treatment of colds, coughs and influenza was claimed.

The defendant sent warning letters because of an infringement of his '029 patent. The plaintiff argued that the contested products did not infringe the patent and there was no reference to the patented uses of Cistus incanus in any of her products. The plaintiff sued for non-infringement and the defendant filed a counterclaim. In a first decision the District Court Düsseldorf considered an infringement of the '029 patent, dismissed the plaintiff's claim and ordered the plaintiff not to manifestly arrange, offer, use, import or possess Cistus incanus. This decision was the basis for this appeal. The Court of Appeal overturned the District Court's decision and stated that patent '029 was not directly infringed because the plaintiff's products are not manifestly arranged for the prevention of common cold diseases. Furthermore, there was no reference regarding "reduction of the infectiousness of rhinoviruses" in the product information. Even marketing material promoting the infringing use of the contested products were not relevant because "it is not known if this is recognised at all by recipients" ([85] m.n. 90) and because there was no reference to the infringing use on the product itself. There was no decision on indirect infringement because it had not been alleged by the defendant.

3.1.3 "Chronic Hepatitis C" – District Court Düsseldorf, 14 March 2013, 4a O 145/12 [86]

The plaintiff, Merck Sharp & Dohme Corp. (hereinafter MSD), markets the active substance ribavirin under the brand name Rebetol for the treatment of ongoing hepatitis C infection in combination with interferon alpha.

MSD is the proprietor of the European Patent EP 0 956 861 B1 (the '861 patent) which was applied for in 13 May 1999. The patent claims a "*Combination therapy comprising ribavirin and interferon alpha in antiviral treatment naïve patients having chronic hepatitis C infection*".

The patent has Swiss-type claims. Claim 1 reads as follows:

"The use of ribavirin for the manufacture of a pharmaceutical composition for treating a patient having chronic hepatitis C infection to eradicate detectable HCV-RNA wherein the

pharmaceutical composition is for administering an effective amount of ribavirin in association with an effective amount of interferon alpha, ***characterised in that*** *the ribavirin in association with the interferon alpha is for administration for a time period of 40-50 weeks, the patient is an antiviral treatment naïve patient, and the patient is having a HCV genotype 1 infection and a viral load greater than 2 million copies per ml of serum as measured by HCV-RNA quantitative PCR.*"

The defendants, CT Arzneimittel GmbH and ratiopharm GmbH, belong to the Teva Pharmaceutical Industries Ltd. Group. They are German manufacturers of generic medicinal products. They have marketing authorisations regarding generic versions of Rebetol containing 200 mg and 400 mg ribavirin.

The German affiliate informed the plaintiff 12 June 2012 that the contested embodiments mentioned above were available in Germany. They were marketed for the first time in August 2012. The ratiopharm GmbH advertised its products with marketing materials claiming that its products could be used instead of Rebetol and sales representatives explained this also to doctors personally. The SmPCs and PILs which also claimed an infringing use of the products were later modified and all references to naïve patients, genotype specificity and virus load as claimed in the '861 patent were carved out. Nevertheless the plaintiff sued for (literal) infringement. This was denied by the District Court which saw no infringement of the '861 patent. Although it stated that for infringement the medicinal product does not only have to be manifestly arranged but that a SmPC or PIL mentioning the infringing use could also be a proof of infringement. But since the public available product information did not mention the important characteristics of the patent (i.e. naïve patients, genotype specificity or virus load), the court decided that the patent was not infringed and did not grant an interim injunction.

The mentioned possible prescription and substitution of the generic products by doctors or pharmacists for the patient subgroup claimed in the patent as well as the encouraging statements of the sales representatives or the marketing material to do so could not persuade the court either. It stated that in case of advertisement it was not proven that physicians would pay attention to this material.

There was no decision on indirect infringement because it had not been alleged by the plaintiff.

3.1.4 "Rebate Agreement" (Rabattvertrag) – District Court Hamburg, 02 April 2015, 327 O 67/15 and others [87]

In April the District Court decided in four preliminary injunction proceedings relating to the active substance pregabalin (Lyrica), docket numbers 327 O 67/15, 327 O 132/15, 327 O

140/15 and 327 O 143/15. Since the wording of the judgment is basically the same, only the docking number 327 O 67/15 will be discussed here.

The plaintiff, Warner-Lambert, belongs to the Pfizer group. Pfizer markets the active substance pregabalin in Germany under the brand name Lyrica for the treatment of peripheral and central neuropathic pain in adults, generalised anxiety disorder in adults and as an adjunctive therapy in the treatment of partial seizures with and without secondary generalization in adults with epilepsy since September 2004. In Germany, 45 % of the sales were for treating neuropathic pain, whereas only 1 % were for epilepsy and 8 % for generalised anxiety disorder.

Warner-Lambert is proprietor of the European Patent EP 0 934 061 B3 (the '061 patent) which will expire on 31 July 2016. It has Swiss-type claims relating to the use for treatment of pain as follows:

> *"1. Use of [pregabalin] or a pharmaceutically acceptable salt thereof for the preparation of a pharmaceutical composition for treating pain.*
> *3. Use according to Claim 1 wherein the pain is neuropathic pain."*

The defendant, Hexal Pharma GmbH, is a manufacturer of generic medicinal products. The defendant obtained a marketing authorisation in Germany for its generic version of pregabalin with a skinny label limited to the treatment of the non-patented indications of the reference medicinal product, i.e. Lyrica, epilepsy and generalised anxiety disorder in adults. Hence, the generic product is not approved for the treatment of neuropathic pain.

The defendant won a tender for a rebate agreement according to § 130a Section 8 SGB V for the active substance pregabalin. The rebate agreement was not restricted to the patent free indications epilepsy and generalised anxiety disorder and the defendant did not point out that its product was not approved for the treatment of neuropathic pain and could therefore not be used for this indication.

The plaintiff sent a warning letter on 15 January 2015 which was rejected by the defendant on 23 January 2015.

The plaintiff sued for indirect infringement of its '061 patent. As supportive documents it submitted the decisions of the UK High Court (cf., see section 3.2.1) and the Court of Appeal in The Hague (cf., see section 3.3.3). Warner-Lambert believed that by participating in rebate contracts the defendant offers its product for an infringing use. The District Court followed this and decided that indirect infringement can be found if the substance as such is offered or supplied even if it has not yet been manifestly arranged, i.e. even though the patent protected indication was not mentioned in the label. It stated that the generic product is already manifestly arranged by its manufacture within the jurisdiction of § 129 SGB V. It granted an interim injunction and prohibited the defendant from entering into rebate

agreements with statutory health insurances and related entities without explicitly clarifying to them that its generic pregabalin cannot be used for the treatment of neuropathic pain and therefore cannot be sold or prescribed for this purpose. Warner-Lambert's other claims regarding initiating changes in prescribing software or providing sales information to the plaintiff were dismissed.

An appeal is currently pending (3 U 65/15).

3.2 United Kingdom

Until recently, there had been no court decisions concerning infringement of second medical use claims in the UK. Former indirect infringement cases of the UK Court of Appeal suggested that to infringe *"it was enough if the supplier knew (or it was obvious in the circumstances) at the time of his offer to supply or supply that some ultimate users would intend to use, adapt or alter the "means essential" so as to infringe"* (Grimme Maschinenfabrik GmbH & Co KG v. Derek Scott, Court of Appeal, High Court of Justice, London (2010) EWCA Civ 1110 [88], affirmed in KCI Licensing Inc v. Smith & Nephew plc (2010) EWCA Civ 1260 [89]).

3.2.1 Warner-Lambert Company, LLC v. Actavis Group Ptc EHF & Others (2015) EWHC 72 (Pat) [90]

The claimant Warner-Lambert Company (here Warner-Lambert) is part of the Pfizer group. Warner-Lambert markets the active substance pregabalin under the brand name Lyrica for epilepsy, generalised anxiety disorder and neuropathic pain. Lyrica had global sales in 2013 of about $4.6 billion $ and in the UK alone about $310 million. In the UK, 54 % of the sales were for treating pain (of which 44 % was for neuropathic pain), 2 % for epilepsy, 12 % for psychiatric conditions (of which 18 % was for generalized anxiety disorder (GAD)) and 32 % for unspecified other diseases.

Patent protection for the molecule expired on 17 May 2013. An SPC was obtained which extended patent protection for pregabalin to 17 May 2018, but lapsed for non-payment of fees. Warner-Lambert's data exclusivity expired in July 2014. However, Warner-Lambert is the proprietor of a second medical use patent (EP 0 934 061 B3; hereinafter the '061 patent) which has Swiss-type claims relating to the use for treatment of pain as described above in section 3.1.4.

The defendant Actavis obtained a marketing authorisation in the UK for its generic version of pregabalin, Lacaent, with a skinny label limited to the treatment of the non-patented indications of the reference medicinal product, i.e. Lyrica, epilepsy and generalised anxiety disorder. Warner-Lambert claimed that Actavis would infringe the patent because they considered that Lacaent was still likely to be prescribed for the patented indication, neuro-

pathic pain, and that Actavis was liable for such sales. They applied for an interim injunction.

Warner-Lambert believed that Actavis had to take steps to prevent its generic pregabalin from being prescribed for the treatment of neuropathic pain, because in the UK, not only 83 % of the prescriptions are written by reference to the generic name, but also 95 % of the prescriptions do not refer to the indication and pharmacists are incentivised to dispense the generic version of a branded medicinal product. These steps should include the use of notices on the packaging, agreeing contractual terms with the pharmacies ensuring Lacaent being dispensed to the non-patented indications only, liaising with the NHS to ensure that physicians were instructed to prescribe by reference name to Lyrica for the patented indication and liaising with providers of prescribing software to ensure that physicians were prompted to do so.

In a first decision, the High Court refused the application, holding that a Swiss-type claim required a subjective intent on Actavis' part that the drug would be used for the treatment of neuropathic pain and that Warner-Lambert failed to show that Actavis had aimed the use of Lecaent for the treatment of pain. This was one of the first decisions in the EU on the infringement of a Swiss-type claim.

The Court of Appeal of England & Wales also came to the decision ([2015] EWCA Civ 556 [91]) that a Swiss-type claim is a process claim involving a manufacturing step. But after detailed consideration of earlier case law relating to Swiss-form claims, EPO case law and the decisions of other national courts in Germany and the Netherlands (see above and below) the Court of Appeal rejected the former High Court decision that subjective intention on the part of the manufacturer or importer that the drug would be used in the treatment of the patented indication was necessary for infringement of a Swiss-type claim. Rather, the Court of Appeal ruled, that the mental element required for infringement was "knowledge or reasonable foreseeability" about the end use of a product for the patented use ([91] m.n. 126). However, the Court of Appeal agreed with the High Court decision that the balance of injustice lay in favour of not granting an interim injunction, and hence rejected the appeal. Nevertheless, it was stated that Warner-Lambert did have an arguable case for infringement under this new interpretation.

Generics (UK) Ltd trading as Mylan and Actavis commenced a claim for revocation of the '061 patent on 24 June 2014 and 12 September 2014 respectively. The revocation applications together with Warner-Lambert's infringement claim came on trial at the High Court (Patens Court) on 29 June 2015 [92]. The court found that none of the claims were obvious over any of the prior art but that several claims, including claim 1 and 3, were invalid on the ground of insufficiency. Insufficiency means that the specification is not sufficient to enable the invention to be performed over the whole scope of the claims without undue

burden. It further held that even if claims 1 and 3 were valid, Actavis had not infringed those claims because there was no proper basis for concluding that Actavis could foresee and either the physician or the pharmacist intended that Lecaent would have dispensed for the treatment of pain. At least it decided that Warner-Lambert is liable for making groundless threats of patent infringement proceedings to some of the addressees like the Department of Health, NICE (National Institute for Health and Care Excellence), superintendent pharmacist and others. In these letters Warner-Lambert stated that prescribing and/or dispensing generic pregabalin for the treatment of pain would infringe its patent. The appeal is pending.

Following the very first decision, Warner-Lambert also applied to the High Court (Patents Court) for a mandatory injunction ordering the NHS Commissioning Board to issue guidance that pregabalin should be prescribed by the reference to the brand name when prescribed for neuropathic pain and by reference to the generic name when prescribed for the other non-patented indications ([2015] EWHC 485 (Pat) [93]). The Court granted the mandatory injunction and the NHS in England has consequently issued guidance to the Clinical Commissioning Groups and the NHS Business Services Authority.

3.3 The Netherlands

There have been only a few cases regarding second medical use claims in the Netherlands, but a recent decision concerning a Swiss-type claim gained great attention worldwide.

3.3.1 Schering-Plough Europe v. Teva Pharma B.V. (2010)

This case in 2010, was the first in Europe addressing the efficacy of a skinny label in enabling generic pharmaceutical companies to avoid infringement.

The claimant, Schering, is part of the Bayer group. Schering markets the active substance ribavirin under the brand name Cotronak (now Rebetol) for the treatment of chronic hepatitis C.

Schering was the proprietor of the patent EP 0 956 861 B1 (hereinafter EP 861) which has Swiss-type claims relating to the use for treatment of chronic hepatitis C with the filing date 13 May 1999 (the patent has been transferred to Merck Sharp & Dohme Corp. in 2012). The claims of EP 861 can be summarised as follows [94]:

> *"use of ribavirin in combination with (pegylated) interferon alpha for the manufacture of a pharmaceutical composition for treating a specific subset of patients (naïve patients) having a hepatitis C genotype 1 infection with a viral load greater than 2 million copies per ml serum for a time period of 40-50 weeks."*

The defendant Teva obtained a marketing authorisation in Europe via the centralised procedure on 19 October 2009 for its generic version, Ribavirin Teva Pharma B.V., with a skinny label. Teva carved out the patented indication from the SmPC [95] in Section 4.1 "Therapeutic indications":

> *"Ribavirin Teva is indicated, in combination with interferon alfa […] with all types of chronic hepatitis C* ***except genotype 1*** *[…]"* (Emphasis added).

However, in Section 5.1 "Pharmacodynamic properties" clinical trials relating to the patented genotype 1 indication were mentioned.

Schering alleged that referring to the patented indication in the SmPC qualifies as direct infringement. The court denied this and stated that by excluding the specific patient category Teva's product fell outside the protective scope of the patent [96]. But the court also mentioned that the decision could have been different if it had been proven that because of the clinical research mentioned and the conclusions from that research, Ribavirin Teva nevertheless would have been prescribed for the patented indication, i.e. naïve patients having a genotype 1 infection [96].

3.3.2 Mundipharma Pharmaceuticals B.V. v. Sandoz B.V. (2010) [97]

The claimant, Mundipharma, markets oxycodone formulations by an affiliate, Purdue Pharma LP, in Europe since 1997 under the name OxyContin, in Germany under the name, Oxygesic. Mundipharma markets OxyContin in the Netherlands in 5, 10, 20, 40 and 80 mg doses.

Mundipharma is the holder of the Dutch part of the European patent EP 0 722 730 A1 (hereinafter EP 730) granted on 30 October 2002 on an application of 28 February 1996. EP 730 relates to formulations for the controlled release of oxycodone or a salt thereof, like oxycodone hydrochloride. The controlled release can be accomplished by means of a controlled release matrix or a release controlling coating. These formulations are approved for the relief of moderate to severe pain, e.g. in cancer patients. Claim 1 comprises the following [98]:

> *"1. Use of an oral controlled release dosage formulation for the manufacture of a medicament for substantially reducing the range in daily dosages required to control pain in substantially all human patients, […]*
>
> *a) from 10 mg to 160 mg oxycodone or a salt thereof; […]"*

By decision of 19 June 2008 the Medicines Evaluation Board granted three marketing authorisations to Sandoz, the defendant, for marketing in the Netherlands of generic (matrix) formulations for controlled release of oxycodone hydrochloride (Oxycodone HCl Sandoz retard) in doses of 5, 10 and 20 mg. The patient leaflet of the Sandoz products

relates to the three different formulations, here, among other things, the following is stated:

"The common initial dose is 10 mg of oxycodone hydrochloride at 12-hour intervals."

Mundipharma took the position that the products of Sandoz infringe patent EP 730. In this context Mundipharma relied on the marketing authorisations obtained by Sandoz, the patient leaflet of its products and other things. Mundipharma argued that indirect infringement was committed with the 5 mg dose.

The Court found the patent to be valid and that Sandoz products with the 10 mg and 20 mg formulations infringe the patent. However, indirect infringement by the 5 mg dose of Oxycodone HCL Sandoz retard was not granted because the court stated that a formulation of 5 mg falls outside the range as included in the mentioned feature of claim 1 and therefore outside the scope of protection of the patent. Thus, the marketing, use and production of the 5 mg formulation is basically free, even though Mundipharma made clear – and this is reasonable – that the use of the 5 mg formulation in combination with the same 5 mg formulation would result in a dose of 10 – 160 mg which would be inside the range of the patent. Additionally, it can be taken from the package leaflet that the 5 mg formulation is suitable and intended for such combined use [99]:

"Oxycodone Hydrochloride 5 mg

Adults and children (over 12 years of age)

The usual and initial dose is two prolonged-release tablets (10 mg of oxycodone hydrochloride) in 12 hourly intervals."

But the court argued that in case of risk patients the physician can prescribe a lower initial dose that 10 mg and therefore the product is intended and could be used below the claimed dosage range. The court disregarded the evidence that the majority of physicians would prescribe within the claimed dosage range. The court granted a provisional injunction for the 10 mg and 20 mg products while awaiting the outcome of the appeal in the pending opposition proceedings.

3.3.3 Novartis AG v. Sun Pharmaceutical Industries (Europe) B.V. (2015) [100]

The appellant, Novartis AG, markets the active substance bisphosphonate zoledronic acid under the brand name Zometa as a 4 mg/5 ml concentrate for the preparation of an infusion solution. Zometa is authorised for the treatment of tumour-related hypercalcaemia and the prevention of bone-related complications in patients with advanced tumour disorders. Zoledronic acid was protected as an active substance until 16 May 2013 by the European patent EP 0 275 821 B1 and the corresponding supplementary protection certificate 300058 for the product Zometa. Novartis also offers the medicinal product Aclasta, which, just like Zometa, contains zoledronic acid as its active substance. Aclasta is a 5

mg/100 ml solution for intravenous infusion that is administered once per year for the treatment of osteoporosis. Aclasta is also approved for the treatment of Paget's disease, a rare chronic bone disorder that can lead to enlarged or malformed bones. Novartis is proprietor of the European patent EP 1 296 689 (herein EP 689) for a "Method of administering bisphosphonates" which was granted 21 September 2005. EP 689, containing Swiss-type claims, relates to the use of zoledronic acid or a salt thereof in the preparation of a medicament for the treatment of osteoporosis administered intravenously at least about once a year [101]. Paget's disease is a very rare disorder whereas osteoporosis is a common disease. Also, for the treatment of Paget's disease usually one administration is needed, whereas osteoporosis has to be treated by injections on a yearly basis. Based on estimation by Novartis, 97.3 % of zoledronic acid 5 mg/100 ml will be used for the treatment of osteoporosis, the remaining 2.7 % (which equals 135 units of a total turnover of 5,000 units per year) for the treatment of Paget's disease.

On 29 July 2013 the respondent, Sun, obtained a market licence from the Medicines Evaluation Board (MEB) for The Netherlands with regard to generic zoledronic acid 5 mg/100 ml. The product is approved for the treatment of both, osteoporosis and Paget's disease. On 26 August 2013 Sun requested the MEB to remove the indication osteoporosis by means of a carve out from the SmPC and the PIL for its product. Even though the MEB informed Sun on 27 August 2013 that the application was processed, it is the policy of the MEB that the carve out is not implemented in the digital version of these documents published by the MEB on its website. In October 2013, Sun registered for and won a tender of healthcare insurer VGZ for zoledronic acid 5 mg/100 ml (for home treatment). This means, that the generic product is the only zoledronic acid 5 mg/ml product that is compensated by the VGZ, except for medical necessity. The tender of VGZ made it impossible to register for the zoledronic acid 5 mg/100 ml for a specific indication. The policy of VGZ comprises that one single product is designated for any patient insured with VGZ that are treated with zoledronic acid 5 mg/100 ml, without distinguishing the indication for which it was prescribed.

Novartis alleged that Sun's generic product is suitable and intended for the application claimed in EP 689 and thereby infringes the patent. Novartis claimed in summary that the judge

- Forbids Sun to commit (indirect) infringement of EP 689 by offering or supplying its generic product in the Netherlands, while it knows or should know that the product is going to be used for the treatment of osteoporosis,
- forbids Sun to take part in tenders/agreements for the supply of its generic product, unless the tender/agreement is limited to treatment Paget's disease,
- alternatively, forbids Sun to supply more than 135 units of its generic product,

- sentences Sun to keep administration of the sale of its generic product and
- to inform all insurers that have floated a tender with regard to zoledronic acid 5 mg/100 ml or intend to do so, on the sentencing due to patent infringement and on the fact that Sun may exclusively supply its generic product only for the treatment of Paget's disease.

In a first decision the claims of Novartis were rejected. The Court of Appeal overturned this decision [100] and stated that Sun committed indirect infringement of Patent EP 689. It argued that Sun had unconditionally registered for the tender of the VGZ for the supply of its generic product, irrespective of the indication it would be used for. Furthermore, Sun committed itself to supply unlimited quantities of zoledronic acid 5 mg/100 ml. On the basis, that all patients that are insured with VGZ get zoledronic acid 5 mg/100 ml, get supplied with only one product without distinguishing the indication, it is inevitable that the generic product will also, and even for the vast majority, be prescribed and supplied for the treatment of osteoporosis which is patent protected. Additionally, the amount of sales indicated that Sun's product was supplied and used not only for the patent free indication. Sun should have done everything possible to prevent its generic product form being supplied for the patented indication. After being warned by Novartis, Sun did send an e-mail to wholesalers and pharmacists, but with the heading "This announcement pertains to formality". In the e-mail Sun stated that its product is currently only intended for the treatment of Paget's disease and that the indication osteoporosis is not included in the PIL for patent reasons. The court found this insufficient because it was not made clear that it was not allowed to prescribe and supply Sun's product for the treatment of osteoporosis and in view of the heading a suggestion of no importance was made. The court stated also, that Sun should have tried to convince VGZ to change its tender, for instance by dividing into different indication for zoledronic acid 5 mg/ 100ml. Sun was sentenced to write to all insurance companies and hospitals that have floated a tender in which Sun has participated and all parties that have concluded an agreement with regard to its generic product. In this letter, Sun had to state that with regard to the indication osteoporosis, it could no longer supply or participate if it was not guaranteed that the use of its generic product for osteoporosis was prevented. Other claims by Novartis were denied.

3.4 United States of America

In the United States a series of Federal Circuit cases has put the balance in favour of generic medicinal products by ruling that for infringement at least one patent protected use has to be mentioned in the generic label. For inducement of infringement, the generic company must have taken active steps, such as promoting the drug for infringing uses. "Specific intent" or the pure knowledge that the medicinal product might be used in an infringing way is not enough.

3.4.1 Warner-Lambert Company v. Apotex Corporation and others (2003) [102]

This was the first decision in the United States to make the use of Section viii certifications possible.

The plaintiff-appellant, Warner-Lambert Company (herein Warner-Lambert), markets the active substance gabapentin under the brand name Neurontin for the treatment of seizures in adults with epilepsy since 1993. Significantly, the FDA has not approved gabapentin for any additional uses. Neurontin, however, was also prescribed and used off-label for the treatment of neurodegenerative diseases with more than three-quarters of all prescriptions being for indications other than epilepsy.

Warner-Lambert is the proprietor of several patents regarding gabapentin. Expired U.S. Patent No. 4,024,175 was the compound patent. A second patent, expired U.S. Patent No. 4,087,544 claimed a method of treating certain cranial dysfunctions, such as epilepsy, with gabapentin. A third patent, U.S. Patent No. 5,084,479 (hereinafter "the '479 patent) claims the use of gabapentin for the treatment of neurodegenerative diseases such as stroke, Alzheimer's disease, Huntington's disease, and Parkinson's disease. Interestingly, Warner-Lambert did not hold a patent for the FDA-approved treatment of adult seizures.

The defendant-appellee, Apotex Corporation (hereinafter Apotex), filed an ANDA in 1998 seeking approval for a generic version of gabapentin upon the expiration of Warner-Lambert's '479 patent on 16 January 2000. As mandated by law, Apotex sought approval only for the same indication for which Neurontin was approved, i.e. for *"adjunctive therapy in the treatment of partial seizures with and without secondary generalization in adults with epilepsy."* [102]. Along with its ANDA, Apotex filed a paragraph IV certification (for explanation, see section 1.4.3.2), asserting that its proposed manufacture, use, and sale of its generic medicinal product would not infringe Warner-Lambert's '479 patent because it was indicated only to the treatment of adult seizures with no reference to the treatment of neurodegenerative diseases anywhere in the labelling. As required by law, Apotex notified Warner-Lambert that it had filed the ANDA and paragraph IV certification.

In response, Warner-Lambert filed an infringement suit alleging that Apotex's generic gabapentin would infringe the '479 patent because of the wide-spread off-label use of gabapentin for the treatment of neurodegenerative diseases and the commonly and routinely substitution of a generic for all indications the brand name medicinal product is used for. In a first decision, the court followed Warner-Lambert's opinion. In a second decision, the court decided in favour of Apotex.

The court of appeal agreed with Apotex, holding that infringement under section 271(e)(2) of the Hatch-Waxman Act (*"It shall be an of infringement to submit (A) an application under section 505(j) of the FD&C Act or described in section 505(b)(2) of such Act for a drug claimed in*

a patent or the use of which is claimed in a patent […] if the purpose of such submission is to obtain approval under such Act to engage in commercial manufacture, use, or sale of a drug, […] claimed in a patent or the use of which is claimed in a patent before the expiration of such patent.") was limited to approved uses of a medicinal product ([102], p. 17, 2nd paragraph). Both gabapentin and its only approved use were off-patent. Because Apotex did not (and could not) submit an application to sell a drug for treatment of neurodegenerative diseases, which is the only use covered by a patent involved in this case, the court concluded that Apotex was entitled to summary judgment of noninfringement. The "mere knowledge of possible infringement by others", i.e. Apotex knowing that its generic medicinal product could be used for the patented treatment of neurodegenerative diseases without promoting or encouraging physicians to do so, was not enough to prove specific intent to induce infringement, also. So, the Federal Circuit denied that Apotex was liable for induced infringement.

Although formally labelled as a "Paragraph IV certification", the Federal Circuit noted, that Apotex's statement regarding the neurodegenerative method patent was effectively a statement of non-applicable use based on 21 U.S.C. § 355(j)(2)(a)(viii) (i.e. a "Section viii certification", for explanation see section 1.4.3.2). With this case, the use of a Section viii certification was validated.

3.4.2 AstraZeneca Pharmaceuticals LP v. Apotex Corp. and others (2012) [103]

The plaintiff-appellant, AstraZeneca, markets the cholesterol-lowering active substance rosuvastatin calcium under the brand name CRESTOR for the treatment of heterozygous familial hypercholesterolemia (HeFH) and to lower the cardiovascular disease risk for individuals with elevated circulating C-reactive protein (CRP) since 2003. In addition to these two indications, CRESTOR is also approved for the treatment of patients with homozygous familial hypercholesterolemia (HoFH) or hypertriglyceridemia. The first two indications are covered by a patent, the last two are not.

AstraZeneca is the proprietor of three relevant patents. U.S. Patent RE37,314 (the '314 patent) claims rosuvastatin compounds, which expires in 2016. U.S. Patent No. 6,858,618 (the '618 patent) claims methods of using rosuvastatin compounds to treat HeFH and U.S. Patent No. 7,030,152 (the '152 patent) claims methods of using rosuvastatin compounds to lower the cardiovascular disease risk for individuals who have normal cholesterol levels but show elevated circulating CRP. The '618 patent expires in 2021 and the '152 in 2018.

The defendants-appellees, the generic manufacturers Apotex and others (hereinafter Apotex) filed ANDAs to market generic rosuvastatin calcium with restriction to the treatment of only HoFH and hypertriglyceridemia while carving out the patented indications HeFH and elevated CRP. In their ANDAs they included Section viii statements (for explanation, see

section 1.4.3.2) affirming that their ANDAs excluded all uses claimed in the ‘618 and ‘152 patents.

In prior litigation, AstraZeneca sued the defendants for infringement of its ‘314 compound patent, which the district court found valid, enforceable, and infringed. These determinations are the subject of another appeal. While this litigation remained pending, AstraZeneca sued Apotex for infringement of the two method of use patents, which gave rise to this appeal. AstraZeneca alleged that the filed ANDAs infringed and would cause infringement of the ‘618 and ‘152 patents, even though Apotex had not requested approval for any patented indications and filed Section viii statements to that effect. First, the Court rejected this view of § 271(e)(2) (for wording, see section 3.4.1) and stated that it is not necessarily an act of infringement to submit an ANDA for a medicinal product *“if just <u>any</u> use of that drug is claimed in a patent”* [103]. The Court held that for infringement, filing an ANDA wherein at least one use listed in the ANDA is patent protected is required. Second, the Court disagreed with AstraZeneca’s opinion, that Warner-Lambert v. Apotex (see section 3.4.1) only applies to patent protected uses, that were not approved or off-label. It rather held that whether or not the carved out indication was approved or not was irrelevant. The only analysis whether an ANDA infringes a patent or not is the scope of the indications applied for in the ANDA without regard to whether the carved out indication had also been approved by the FDA because generic applicants cannot obtain approval for uses other than those already approved. AstraZeneca’s argument that Section viii statements and restricted generic labelling ignored market realities because even if a generic medicinal product is formally approved only for unpatented uses, pharmacist and physicians will nonetheless substitute the generic for all indications of the innovator medicinal product found the Court unpersuasive. The district court’s judgment dismissing the complaint was therefore affirmed.

3.4.3 Bayer Schering Pharma AG v. Lupin, LTD. (2012) [104]

The plaintiff-appellant, Bayer Schering Pharma AG (hereinafter Bayer), markets the oral contraceptive, Yasmin, with the active substance drospirenone since 2001. The FDA-approved label states in the Indications and Usage sections that “*Yasmin is indicated for the prevention of pregnancy in women who elect to use an oral contraceptive.*” [104]. The Pharmacodynamics subsection of the Clinical Pharmacology section recites that drospirenone is “*a spironolactone analogue with antimineralocorticoid activity. […] Preclinical studies in animals […] have also shown that drospirenone has antiandrogenic activity*.” [104].

Bayer is the proprietor of U.S. Patent No. 5,569,652 (the ‘652 patent). The ‘652 patent is a method-of-use patent with two independent claims claiming three different effects: a contraceptive (or gestagenic), an antiandrogenic, and an antialdosterone (also known as an anti-mineralocorticoid) effect in a premenopausal or menopausal female patient.

The defendant-appellee, Lupin und others (hereinafter Lupin) had filed ANDA applications to market generic versions of Yasmin for oral contraception in 2010. The ANDAs were accompanied by Paragraph IV certifications, stating that the patents listed in the Orange Book were either invalid or would not be infringed by the generic product.

Bayer filed a complaint against Lupin in July 2010 alleging infringement of patent '652. The district court held that because the FDA had approved the use of Yasmin only for contraception, and not for the simultaneous treatment of all three conditions, the '652 patent was not infringed. That gave rise to this appeal.

Bayer does not hold a patent for the use of Yasmin for contraception alone. But Bayer contended that the FDA approved the use of Yasmin for all three effects as demonstrated by the label. Therefore, the generic versions of Yasmin likewise covered the use for treatment of all three effects simultaneously and the defendants were liable for inducing infringement by physicians and patients. This was denied by the district court and confirmed by the Federal Circuit. The Federal Circuit stated that the reference in the Clinical Pharmacology section was due to regulatory regulations and not a direct indication nor an implied or suggested indication of an appropriate use. In addition, the labeling regulation, 21 CFR §201.57, states that such implied or suggested uses do not constitute approved uses. The Federal Circuit continued that "*the label, taken in its entirety, fails to recommend or suggest to a physician that Yasmin is safe and effective for inducing the claimed combination of effects in patients […]*" [104]. Four pieces of evidence, including a declaration of a physician and one from a former FDA official, that Bayer relied on to support its argument that the references to antimineralcorticoid and antiandrogenic acitivity in the Clinical Pharmacology section indicated FDA approval of Yasmin to induce those effects could not persuade the Court. The Court found that this demonstrated only that the FDA was aware of Yasmin being able to cause these effects.

Finally, the Federal Circuit indicated that Lupin's ANDA seeks approval to market the generic form of Yasmin only for contraceptive use despite the evidence for inherently infringement of Bayer's patent by the generic products. Since there is no valid method of use patent for that purpose alone, the generic medicinal products cannot infringe the '652 patent or any other patent. Therefore, the Federal Circuit agreed with the dismissal of Bayer's claims for infringement by the district court.

3.4.4 Caraco Pharmaceutical Laboratories v. Novo Nordisk A/S (2012) [105]

In this case, the Supreme Court of the United States decided whether the Congress has authorised a generic company under 21 USC §355(j)(5)(C)(ii)(I) to challenge a use code's accuracy by bringing a counterclaim against the brand manufacturer in a patent infringement suit.

Novo Nordisk A/S (hereinafter Novo) markets the active substance repaglinide under the brand name Prandin for the treatment of diabetes. The FDA has approved three uses of Prandin: repaglinide by itself, in combination with metformin and in combination with thiazolidinediones (TDZs).

Novo is the proprietor of two patents regarding repaglinide. Expired Patent No. RE37,035, (the '035 patent) which claimed the compound itself and expired in 2009 and U.S. Patent No. 6,677,358 (the '358 patent), which claimed the method of using repaglinide in combination with metformin and expires in 2018. But Novo held no patent for the use of repaglinide with TDZs or its use alone.

In 2005, the petitioner, Caraco Pharmaceutical Laboratories. (hereinafter Caraco) filed an ANDA, assuring the FDA that it would not market its generic product until the '035 (compound) patent expired. When Caraco filed this ANDA, Novo's use code regarding the '358 patent indicated that the patent covered the "*use of repaglinide in combination with metformin to lower blood glucose*" ([105] at 1679). Caraco filed a Paragraph IV certification against the '358 patent. Novo filed an infringement suit. In 2008, on advice from the FDA, Caraco converted its Paragraph IV certification into a Section viii statement, carving out the patented metformin combination therapy and applying only for the two, patent free uses.

Soon thereafter, and before the FDA took further steps, Novo changed its use code for the '358 patent. The new use code described a "*method for improving glycemic control in adults with type 2 diabetes*" ([105] at 1679). This broader code now comprised all three approved methods for treating diabetes with repaglinide. The FDA takes a code as given and does not assess the patent's scope. Additionally, it will not approve an ANDA if the proposed carve-out label of the generic manufacturer overlaps with the use code of the brand. Consequently, the FDA rejected Caraco's ANDA.

In response, Caraco filed a statutory counterclaim, which was introduced into legislation by the "Medicare Prescription Drug, Improvement, and Modernization Act" of 2003. The provision (21 USC § 355(j)(5)(C)(ii)(I) [43]) authorised an ANDA applicant sued for patent infringement to

> "*assert a counterclaim seeking an order requiring the patent owner to correct or delete the patent information filed by the patent owner under subsection (b) or (c) [of § 355] on the ground that the patent does not claim – (AA) the drug for which the application was approved; or (BB) an approved method using the drug*."

The counterclaim sought an order requiring Novo to restore its use code on the ground that two approved methods for the use of repaglinide, i.e. combination with TDZs and alone, are not claimed by the '358 patent. The district court followed this view and ordered Novo to correct its inaccurate description of the '358 patent. The Court of Appeal re-

versed, saying that the statutory phrase "the patent does not claim…an approved method of using the drug" meant that "the patent does not claim … **any** method of using the drug". Because the patent covers one approved method to use repaglinide in combination with metformin, the counterclaim was not appropriate. Caraco read this phrase as "an approved method" meaning "a particular method". The Supreme Court held that both interpretations were true, depending on the context. But in this case it agreed with Caraco – and thereby reversed the judgment of the Court of Appeals again – that "an approved method" meant "a particular approved method". The interpretation of "a method" meaning "any method" would prevent marketing of generic versions of branded medicinal products as long as one patented use of the branded products exists. The Supreme Court held that this was not the intention of the Congress and therefore the counterclaim was established to force NDA holders to amend their inaccurate use codes listed in the Orange Book.

3.4.5 Hospira, Inc., et al. v. Sylvia Mathews Burwell, et al. (2014) [106]

This case is not like the others listed before between two (or more) pharmaceutical companies. Here, Hospira, an innovator company, and Sandoz, a generic company, sued the FDA for violation of the Hatch-Waxman Amendments by approving other generic versions of a certain medicinal product. Nevertheless, it deals with skinny labelling.

The plaintiff, Hospira, markets the active substance dexmedetomidine hydrochloride under the brand name Precedex for two separate indications: (1) "*sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting*" ("*Intensive Care Unit Sedation*"); and (2) "*sedation of non-intubated patients prior to and/or during surgical and other procedures*" ("*Procedural Sedation*").

Hospira is the proprietor of several patents covering Precedex. The only relevant patent is a method-of-use patent: U.S. Patent 6,716,867 (the '867 patent), which expires in 2019. Hospira listed this patent in the Orange Book in 2004 with the following use code: "*Intensive Care Unit Sedation*." In November 2008, Hospira listed U.S. Patent No. 5,344,840 (the '840 patent) with the following use code in the Orange Book; "*Sedation of non-intubated patients prior and/or during surgical and other procedures*." However, the '840 patent expired in 2011. Thus, the '867 patent is the only relevant patent in this case.

This case involves three ANDA applicants: Plaintiff-Intervenor Sandoz, who pursued generic Precedex approval through the Paragraph IV certification process; and Defendant-Intervenors Mylan and Par Sterile who sought and obtained approval to market and sell generic Precedex through a Section viii statement.

Sandoz submitted an ANDA in 2009 including a Paragraph IV certification. Since this was the first ANDA including a Paragraph IV certification, Sandoz was entitled to the 180-day generic market exclusivity explained above in section 1.4.5.2. After the consequent notifi-

cation, Hospira sued Sandoz for patent infringement. In 2013, after more than three years of litigation, Sandoz and Hospira entered into a settlement agreement under which Sandoz was allowed to market its generic Precedex product in December 2014.

Several other generic manufacturers, including Mylan and Par Sterile, submitted ANDAs including Section viii statements. Mylan submitted its ANDA in February 2011, while Par Sterile submitted its ANDA in February 2012. Both carved out the listed use of, and all explicit references to, "*Intensive Care Unit (ICU) Sedation*" from their proposed label (i.e. product information) for their products, leaving only references to "*Procedural Sedation*", which was off-patent.

In March 2013, the FDA gave tentative approval of the ANDAs with 15 January 2014 as the date for the final approval, because then another patent of Hospira covering Precedex expired. Shortly before this final approval, however, Hospira sought to amend the listed '867 patent use code from "*Intensive Care Unit Sedation*" to "*Intensive Care Unit Sedation, including sedation of non-intubated patients prior to and/or during surgical and other procedures*." Hospira explained that this amendment was only meant to clarify without broadening its original use code. Hospira also explained that the new use code now overlapped partially with the second indication (Procedural Sedation), in case such sedation occurs in an ICU. As stated above in Caraco v. Novo Nordisk, the FDA cannot approve an ANDA, if the generic's proposed carve-out label overlaps with the use code of the brand. Based on this, Hospira requested the FDA not to approve ANDAs containing a Section viii statement.

The FDA rejected Hospira's request and determined that as long as all references to the use protected by the '867 patent (ICU Sedation) are properly carved out, it could approve an ANDA with a Section viii statement even though broad, general indications might partially overlap with a protected method of use. The FDA argued that this was the case with the respective ANDAs.

Hospira immediately filed suit in district court seeking an injunction staying the FDA's decision. The court followed the FDA's assessment. It held, that approval of the ANDAs despite the fact of partial overlaps was correct and consistent with the approval of other ANDAs regarding substances with a broad indication as long as all references to a protected use are carved out properly. It stated also, that Caraco did not apply here because it concerned a complete and coextensive overlap between a broadened use code with a single indication. Even the given evidence that physicians might use the generic version of Precedex in an ICU, also acknowledged by the FDA, did not persuade the court. Therefore, the court denied Hospira's claims and granted Summary Judgment to the FDA.

4. Discussion

The focus of the health care industry and its legislation should be on improving public health, i.e. on the patient and the patient's need for the best possible therapy at the best possible price. This superordinate overall goal will be the centre of the following discussion. However, paradoxically, the patient, even though the main focus, has only a negligibly small impact on the overall system. The following discussion will rather show that it will be the main task of the health authorities/legislation to establish the mandatory rules and regulations to achieve this goal and simultaneously safeguard the specific interests of all stakeholders. Elements of the US system that could help to improve the situation in Europe will also be discussed. The discussion will further highlight that the physician, who creates the nexus between the stakeholders, will have an important role in this scenario.

Hereinafter the stakeholders will be discussed along the use chain of a medicinal product in an ascending order – starting with the:

4.1 Patient

The patient has the strongest, because personal, interest in medicinal products that have a high safety, efficacy and quality level but is also interested in low prices and co-payments. But today's policy of mandatory or highly incentivized substitution poses a not to be underestimated risk for the patient's health. The patient sees his doctor for a cure to his disease or condition. The doctor prescribes a medicine but the patient does not necessarily get this specific medicine at the pharmacy. Rather, the dispensed medicinal product depends on the price or which pharmaceutical manufacturer is the partner in the rebate agreement with the patient's statutory health insurance. Thus, neither the doctor nor the patient knows which medicine the patient actually receives. So it is not unlikely that the patient receives a medicinal product that in fact contains the same active substance as prescribed but it possibly does not only differ in shape, colour, size or dosage form but is not approved for the disease or condition in question. The SmPC and PIL of such medicinal product contain all the information regarding indications, contraindications, doses, type of application and frequency of administration but only for the approved indications. Such information can therefore differ significantly between the various indications.

The level of the differences and the resulting risks are shown by medicines containing the active substance bisoprolol. Bisoprolol is a beta blocker. Depending on the manufacturer, medicinal products containing bisoprolol are approved for the treatment of high blood pressure and angina pectoris [107] or for the treatment of high blood pressure, angina pectoris and heart failure [108]. Even worse, the products approved only for the first two indications state that heart failure is a contraindication and the medicine should not be taken by patients suffering from this condition. Additionally, the PIL of the products ap-

proved for heart failure contain an extensive dosing regimen explaining the gradually ascending dose necessary for the treatment of heart failure. This is missing completely in the PIL of products not approved for heart failure. Possibly, if a patient suffering from heart failure receives a bisoprolol product which is not approved for this condition, will not take the medicine because the indication is not mentioned in the PIL or is even listed as a contraindication. This could lead to a worsening of his or her condition. And even if the patient uses the medicinal product despite this information, he or she might take a lower or higher dose because he or she is not informed about the necessary titration. This could lead to therapy failure or in case of higher doses to a higher risk of adverse events. Other examples, in addition to the ones already mentioned above in section 3, for different indications of medicinal products containing the same active substance are:

Active substance	Product A – Indications	Product B – Indications
Clopidogrel	• Prevention of atherothrombotic events (adult patients suffering from myocardial infarction, ischaemic stroke or established peripheral arterial disease; adult patients suffering from acute coronary syndrome) • Prevention of atherothrombotic and thromboembolic events in atrial fibrillation [109]	• Prevention of atherotrombotic events (patients suffering from myocardial infarction, ischaemic stroke or established peripheral arterial disease [110]
Leflunomide	• Treatment of active rheumatoid arthritis • Treatment of active psoriatic arthritits [111]	• Treatment of active rheumatoid arthritis [112]
Ropinirole	• Treatment of Parkinson's Disease • Treatment of moderate to severe idiopathic Restless Legs Syndrome [113]	• Treatment of moderate to severe idiopathic Restless Legs Syndrome [114]
Valsartan	• Treatment of high blood pressure • Treatment of symptomatic heart failure • Treatment of adult patients after a recent heart attack [115]	• Treatment of high blood pressure • Treatment of symptomatic heart failure [116]

Table 1: Different indications of medicinal products containing the same active substance

Compliance is a problem in the treatment of chronic diseases as such. Studies show that patients with chronic diseases take only about 50 % of the prescribed medicines [117]. But issues as mentioned can contribute to this problem. The German Federal Ministry of Health (Bundesministerium für Gesundheit) together with the German Medical Association

(Bundesärztekammer) issued a brochure “Tips for a safe drug therapy” (*Tipps für eine sichere Arzneimitteltherapie*) [118]. In this brochure it states that information regarding application and administration of medicinal products can be found in the PIL. With substitution of a medicinal product which is not approved for the specific indication the patient has no chance to get such information from the PIL.

The carving out of references to patent protected indications in all sections includes another risk to the patient’s safety. Even though the Q&A section on generic and hybrid applications [63] recommends to keep safety-related information in sections 4.3 to 4.8 of the SmPC when deleting patent related information, this is not always done by the generic companies as this is optional. Instead, even safety-related information is deleted if it refers to patent protected indications. By this means, important information is missing which should contribute to the patient’s safety.

In Europe, the patient is not liable for infringement because in all national laws patents do not extend to private use. In the US, private use is not exempted because 35 USC 271 [44] states that “*whoever […] uses […] any patented invention […] infringes that patent*”. There is no distinction between private and nonprivate use.

In all countries with mandatory or highly incentivised substitution the patient has no influence on the medicine that he receives at the pharmacy. The situation is a little better in some states in the US because there the patient has to give his consent on substitution. Even in Germany, the patient has the choice to pay the remaining difference if he wants to get the brand medicine instead of the generic. But this decision is also driven by financial not by medical reasons – co-payment depends on the pharmacy retail price. It also cannot be the patient’s duty to know the medical or regulatory background of a medicinal product. And the best possible therapy for someone should not depend on his financial capability. But as mentioned in the beginning of this section, the patient has no chance to change this system.

4.2 Pharmacist

The pharmacist is in a no better situation. The pharmacist is bound by law or high incentives to substitute a generic or rebated medicinal product if this is not explicitly prohibited by the prescribing doctor. Without an indication on the prescription the pharmacist is not aware whether he dispenses a medicine for a patent protected indication and thereby contributes to patent infringement. Even if it is indicated by the pharmacy software that dispensing a generic medicinal product for certain indications is prohibited, there is no way to find out for which disease the medicine was prescribed for.

In 2009, the Higher Regional Court Hamburg decided that in cases where a brand medicinal product and its generic differ in indications the pharmacist has to make sure that the

generic product is not dispensed for an indication it is not approved for [74]. This is illusory. There are two possible approaches for this task which are both ignoring reality. First, the pharmacist could call the doctor asking for the indication reason the medicine is prescribed for. The doctor is not allowed to tell anybody about the underlying diagnosis because of his medical secrecy. Plus, it is not clear how the pharmacist should identify himself to the physician even if the doctor was allowed to tell him. This would open the door to abuse and put more pressure on the relationship between doctor and patient. The second approach would be to directly ask the patient. But this does not lead to the desired result either. The patient could give a wrong answer whether due to fraud or error or does not answer at all. It must be assumed that some patients really do not know why they have been prescribed a certain medicine or in case of various medicines, why each of them was prescribed. And of course the patient could give a wrong answer intentionally or does not answer the pharmacist's question at all. So it does not make sense to ask if a useful answer cannot be expected. But even if one of these approaches would work are they way too inconvenient and time-consuming.

In Germany, the pharmacist can reject the substitution if he claims pharmaceutical concerns. This could be done in case of a suspected patent infringement. But since the pharmacist bears the risk of financial penalties ("*Retaxierung*") in case of unjustified pharmaceutical concerns, he will be reluctant to do so. But dispensing a generic medicinal product for a patented indication for which it is not approved can qualify as (contributory) patent infringement, both in Europe and in the USA. It must be clarified which rule of law prevails – social law or patent law. However, like the patient, the pharmacist has little to no influence of changing today's system.

4.3 Physician

Bound by his oath, the physician is interested in improving public health but has of course also monetary reasons. He is the only member in this system who actually knows the disease or condition of a patient and the appropriate treatment. It is not acceptable that the doctor does not know which medicine his patient actually receives at the pharmacy. Doctors are the link between the patient on one hand and the pharmaceutical industry/health care authorities on the other. They should be "*free to use their skills and knowledge of the available treatments to achieve the utmost benefit for their patients uninhibited by any worry that some treatment might be covered by a patent*" (EPO Enlarged Board of Appeal Case Number G 0001/07; [119]). But they are not for various reasons. First of all, they are not free because of budgetary limitations and managed care models. They will have to prescribe generic medicinal products if they want to be regarded as cost-effective and not become subject to recourse claims. Statutory health insurance physicians have to meet certain target figures for prescribing generics. Prescription computer programs encourage generic

prescribing. In almost all cases the physicians are not aware of all the indications a generic medicine is approved for. In the UK, physicians are rewarded if they switch a patient to a cheaper generic medicine.

Second they are not free because they act commercially and are thus not exempted from patent infringement (decisions of the District Court Hamburg and the Upper District Court Munich, [27]. This is because the physician's freedom of therapy is provided by an exclusion of medical methods from patentability rather than an absolute use privilege. Because physicians operate within a commercial context they cannot rely on the private use privilege. While a Swiss-type claim could not be infringed by a doctor in the normal daily practice because they are process-claims and always include a manufacturing step ("manifestly arrangement"), the new EPC2000 claims can be infringed. EPC2000 claims, being purpose-limited product claims are realised by a doctor prescribing a medicinal product for an infringing use. Even though there is no case law on this matter, it should be kept in mind.

In the US, as said above for the patient, any party in question (manufacturer, physician, pharmacist and patient) can be liable for infringement, thus also the prescribing physician. In a recent decision, the U.S. District Court of the Southern District of Indiana held that physicians directly infringe a patent by directing and controlling the administration of a certain patent protected substance [120]. But since physicians have to respect patents in the medical sector in general there is no reason why this should be different for second medical use inventions.

Because of their expertise and their knowledge the physicians should be the key to provide the best possible treatment and therefore improve public health while preventing patent infringement of second medical use claims. Unfortunately they are not able to do so at the moment due to legal and monetary restrictions. The possible measures of the physicians to influence the existing system today are limited. In section 4.6 the necessary changes will be listed to allow the physician's key role.

4.4 Generic companies

Generic companies have a strong commercial interest in the improvement of public health. But this interest is not sufficient because it overrides all other interests.

Generic manufacturers provide medicinal products at a low price to reduce health care costs. European and US regulatory legislation is drafted to facilitate market access of generic medicinal products as soon as the first period of patent protection/exclusivity of the brand medicinal product expires. Because real regulatory legislation/guidance regarding the consideration of second medical use claims and skinny labelling is missing, the generic companies deal with an uncertain legal situation. The possible carve-out of patent protected indications in the product information of a generic medicine implemented in the

European and US regulatory legislation allows the early market entry of a generic product even if other indications are still covered by a patent. These carve outs ignore market realities. Due to mandatory and permissive substitution laws or by other means supported substitution it is almost inevitable that a generic medicinal product is dispensed for an indication it is not approved for. Such situation leads to legal proceedings in a developing field of law.

In some cases the market share of the second (or further) medical use is larger than of the first. Therefore, the generic manufacturer may not intend or even foresee infringing an innovator's patent but the impression is created that its infringing use is approvingly accepted by some manufacturers. The common excuse is that the generic manufacturer has no way to influence the system. But it should be self-evident that property rights of the innovator companies are respected. Therefore, all measures should be avoided that create the opposite impression, like unconditional participation in a tender irrespective of the indication for which the product is going to be used. It could also be expected that the generic manufacturer takes proactive measures to prevent its products from being used in an infringing way. This could be achieved by notifying health care authorities, health insurances, pharmacists and software providers that the generic product cannot be used for certain indications. Also the physicians could be informed that the generic medicine cannot be prescribed for certain indications. But most likely no company will make such an effort voluntarily without legal guidance.

The blue box concept used in some countries is discussed controversially. In the UK, for instance, the generic company has to print in its PIL that its product might be authorised to treat other conditions that are not mentioned in the PIL. For further questions the patient should ask his/her doctor or pharmacist. On the one hand it is said that this wording provides reassurance to patients receiving a generic medicine dispensed for a carved out indication. The opposing argument is that this wording contributes to patent infringement by emphasizing that the generic product can also be used for other indications.

A removable label on the transport packaging or outer packaging stating that the medicine should not be dispensed for a certain indication as claimed in Warner-Lambert v. Actavis in the UK could also be a solution worth thinking about. This would increase awareness of patent protection. On the other hand it would probably not help the pharmacist to know whether the presented prescription has been written for a protected indication. Such labels are not allowed at the moment anyway because they do not comply with Directive 2001/83/EC. The views within the EU are divided on this question. Also in the USA such a label is not planned.

Considering the risk of costly legal proceedings the generic companies will most likely be willing to amend the existing procedures and measures but legal guidance is needed.

4.5 Innovator companies

Like the generic companies, the innovator companies have a strong commercial interest in improving public health but unlike generic companies do they contribute to this goal by making significant investments in research and development. It has been increasingly recognised over the past decades that finding second (or further) uses for established substances makes an important contribution to improving public health because they may find solutions for unmet medical needs and provide substantial benefits to patients. But the costs for development and approval of a new use are only a little less compared to those for a new substance. The patent protection granted for such an innovation is weakened by mandatory or permissive substitution, skinny labels and other measures supporting the generic industry. The innovator companies do not have a chance to recoup the high investments made.

The inventions of new uses do not seem to be appreciated. But there are no second-class patents. Article 27 of the TRIPS Agreement states that patents shall be available for any inventions in all fields of technology. Patent rights shall be enjoyable without discrimination [121]. By deciding on second medical use or methods of treatment claims being patentable the issuing countries did not only achieve the right to benefit from these patents but also committed themselves to obligations. Article 41 of the TRIPS Agreement states "*[m]embers shall ensure that enforcement procedures […] are available to permit effective action against any act of infringement*" [122]. However, second medical use claims are difficult to enforce, especially in cases of cross label use and proof of intention and/or knowledge of the generic manufacturer. The respective case law shows that the underlying opinion in most countries is that second medical use or methods of treatment claims are only used to protect the profit of the innovator companies and to ban generic companies from the market as long as possible ("evergreening"). In almost all cases mentioned in section 3 the decisions of the courts were in favour of the generic company even if considerable evidence for generic products used in an infringing way was presented. It seems like the courts are starting to decide a little more in favour of the innovator companies but the outcome of a case is always unpredictable und often incomprehensible. The enforcement of these claims need to be facilitated. For instance, in France it is almost impossible to obtain an injunction when all references to patent protected indications have been carved out from the label. The innovator as well as the generic pharmaceutical need more predictable and better reasoned decisions. This cannot be solved by the companies or the courts alone but only by a better legislative and regulatory framework.

The US model of notifying innovator companies whether or not their products are going to be infringed by a generic product might also be an improvement to the European system. Today, when a patent is approaching the end of its lifecycle, the innovator companies take

costly measures to be prepared in case an infringing generic product enters the market ahead of patent expiry. These expenditures could be used to better effect.

The innovator companies, of course, have obligations, too. To prevent “evergreening”, i.e. a strategy to retain revenues from products with patents that are about to expire, narrow consecutive patents should be avoided. A second medical use claim should be a real invention not an obvious side-effect. This should also be considered when granting patents.

4.6 Health care authorities/statutory health insurances

Health care authorities and health insurances have a strong interest in improving public health, especially with the ever increasing ageing society and their multiple diseases and disabilities of today. But they also have a strong interest in reducing expenditures. The large benefit resulting from the discovery of new uses for known active substances is explicitly requested but the consequential patent protection is not respected and rather minimised. Generic substitution is important und must definitely be maintained for non-patented indications. Nevertheless, the innovator companies’ rights conferred by second medical use patents must also be protected. A balance between the interests of all stakeholders must be found. It was shown in the recent discussion that the only stake holder who has the power to change anything in the current system are the health care authorities and the health insurances.

The most likely source of tension lies within the way in which medicinal products are prescribed and dispensed in most European countries. Unfortunately, this is due to the lack of compatibility between the patent and the regulatory system. The patent system cannot be changed without loss of conferred rights but changes to the regulatory system would allow a better balance.

The safety of the patients has to outweigh commercial or financial interests in general. Therefore, the focus should be on the patient’s benefit. The first and most important measure is to provide binding guidance to physicians to prescribe medicines by brand name for patent protected indications and by generic prescription or INN for the non-patented indications, thereby addressing two objectives at the same time. If medicinal products are prescribed this way, it is not possible that a patient receives a medicine with a lack of information regarding dosage, mode of administration etc. in the PIL. This reduces the risk of confusion and increases compliance while decreasing the risk of dropouts. Additionally, the innovator’s patent rights are protected. This guidance must also be transferred to other stakeholders like health insurances and software providers. Procedures need to be established on how physicians are going to be informed about patent protected indications and how to update the prescribing software. A database, similar to the Orange Book in the US, needs to be established listing all relevant patents concerning a given

reference medicinal product. It contributes to the dispute that patent matters are not considered when applying for approval of a generic medicine especially in an industry that depends on patents as the pharmaceutical industry.

Alternatively, a medicinal product should only be substituted if it is fully consistent with all indications of the brand medicine. This would be in conformity with the decisions of the Higher Regional Courts of Hamburg and Frankfurt.

For both approaches a publicly accessible database needs to be established listing all indications generic medicinal products are approved for.

A blue box concept would not be needed anymore because a generic medicinal product could not be dispensed for an indication it is not approved for.

Until this change in the regulatory system is implemented, there should be compulsory guidance to the statutory health insurances to invite tenders by indication not by substance. This allows generic manufacturers to participate for non-patented indications and respects patent law. In March 2015, the German Federal Cartel Office (Bundeskartellamt) ordered a health insurance to restart a tender procedure for a rebate agreement because one of the indications of the relevant substance was still patent protected. It held that due to the substitution law the generic products offered and supplied under the rebate agreement will be used irrespective of the indication thereby infringing patent law. It also stated that patent law must not withdraw behind social law ([123]).

Also clear and binding guidance – both, national and European- is needed stating which information should be carved out of a generic SmPC and PIL and which information needs to be maintained. Missing information about drug administration, drug-drug-interactions and other warnings and precautions are further safety risks. It cannot be in the interest of the authorities to diminish patent protection and to promote the unsafe use of generic medicinal products.

Also changes in the reimbursement system are required. The brand product should be allowed to be reimbursed at a higher price when being dispensed for the patent protected indication. Also a coding system could be used on the prescription to let the pharmacist know the underlying disease so that the right medicinal product can be dispensed. In both cases budget restrictions and recourse claims have to be lifted because neither doctors nor pharmacists should be punished for complying with patent law. The patient would also be punished if the doctor cannot prescribe a medicine for a patent protected indication or because it is not dispensed by the pharmacist because of monetary reasons.

With respect to facilitating the enforcement of second medical use claims, a definition needs to be provided to indicate which kind of evidence is needed to prove intention or knowledge of an infringing use of the generic manufacturer. The courts should go further

than just analysing the label of a product or to examine if the product was manifestly arranged. Evidence could be e.g. procurement, prescribing and dispensing practices to show probability of cross-label use, relative market share of the different indications, steps taken to promote the drug and to encourage or discourage the infringing use. The fact that there is no reference to the patented indication in the label should not exclude a priori infringement of a patent. If infringement is detected, liability should be determined in the same way as for any other type of patent.

5. Conclusion and Outlook

An amendment to the current system of generic substitution on a legislative and regulatory level is essential. The best solution to the problems occurring with skinny labelling, i.e. protecting the rights of an innovator company conferred by a second medical use patent while allowing generic competition for patent-free indications is to separate the two markets. This can be achieved by ordering the physicians to prescribe by brand name for patent protected indications and by reference to the substance (by INN) for the non-protected indications. Physicians cannot know when this is necessary. What is needed is binding guidance as to when this should be done. Such guidance needs to be transmitted to health insurances and software providers as well. Since a substantial change is likely to take some time and might meet considerable resistance from policy makers, doctors, pharmacists and software providers, for fast results guidance to the doctors on a product-by-product basis could be issued. Finding second (or further) uses for established substances makes an important contribution to improving public health but the number of such patent applications have dropped dramatically in Germany from 2007 to 2013 (from 405 to 13) [83]. If the current support of generic substitution will be curtailed, innovator companies will be incentivised again to develop new uses for known substances without fear of opening new markets for generic companies. This will lead to substantial new investments from which the public will benefit in the end.

6. Summary

Finding new uses for known substances makes an important contribution to improving public health. Patents in form of second medical use claims were established to promote and incentivise this kind of research. Since 2004, it is possible in Europe to market generic medicinal products with carve-outs of patent protected indications or other new uses in their labelling (so-called “skinny labelling”). Many countries have introduced generic substitution to increase the use of generic medicines and thereby reduce health care costs. Thus, the generic medicinal products with a skinny label approved only for non-protected indications/uses are actually dispensed for all indications/uses of the brand medicinal product.

This procedure leads not only to a weakening of patent law but has also an impact on patient’s safety and creates an area of conflict for all stakeholders. Further regulatory legislation/guidance is needed.

In this master thesis on overview of the current system regarding skinny labelling and second medical use claims is presented. Problems arising out of the current practices are discussed and opportunities for an improvement are proposed by a comparison to the US system and by taking into account the recent jurisprudence concerning second medical use claims.

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Erklärung

Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

Bergisch Gladbach, den 23.11.2015 _____

Dr. Andrea Abele