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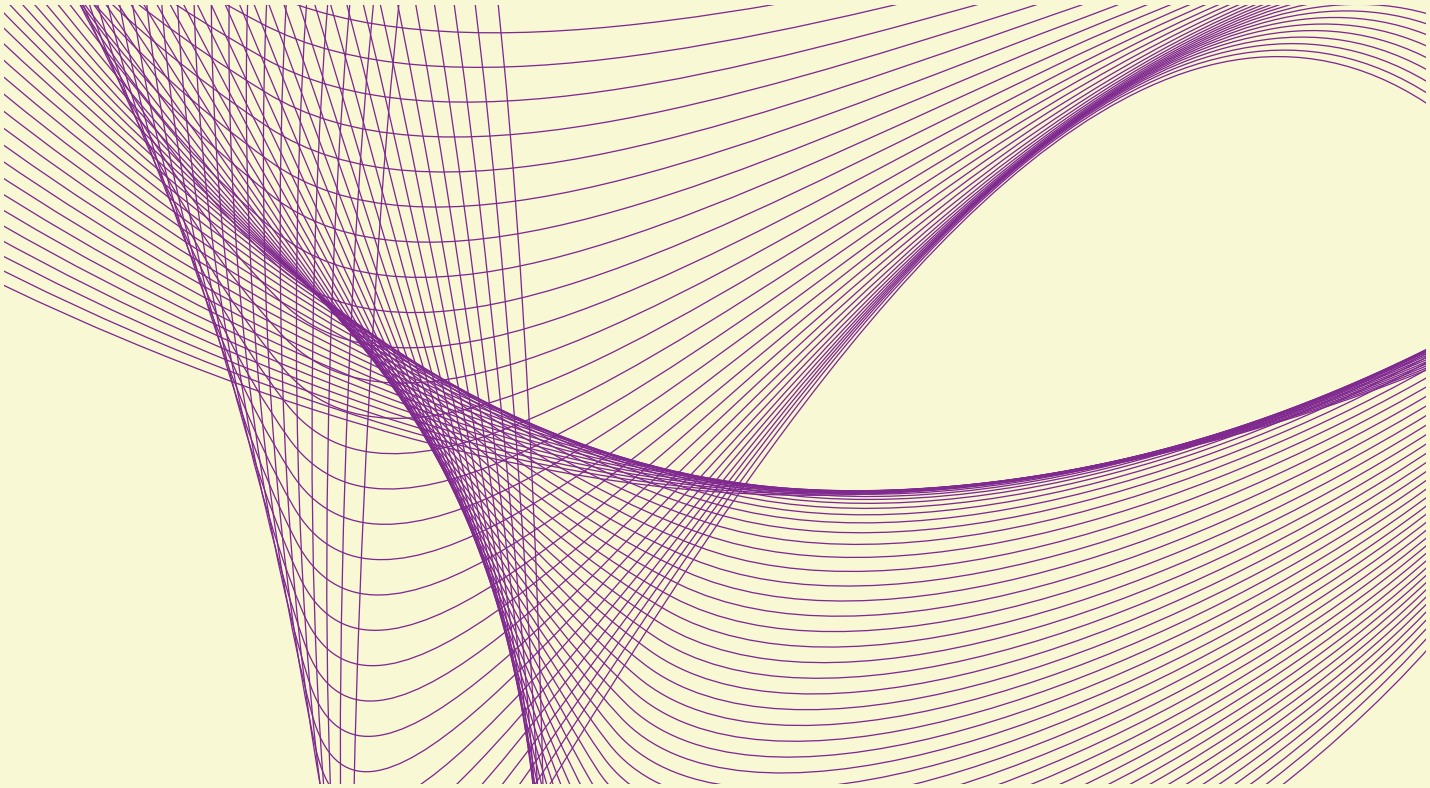

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Editorial Preface

"Some industries are different but some are more different than others. The pharmaceutical industry fits the latter category" (Scherer 1996:336). There is really no other industry where the nature of the products, the economics of research and development as well as the market structure and the societal implications of the industry's strategic decisions are as unique as in the pharmaceutical industry. Furthermore, there is no other industry that tests the boundaries and effects of intellectual property (IP) rights on a national and international level as the pharmaceutical industry.

The current issue of the Stockholm IP Law Review provides an eloquent presentation of pharma-related IP challenges exploring these from different angles and perspectives.

Genetic engineering is one of the major challenges in modern pharmaceutical research. It opens up for revolutionary therapeutic applications and represents considerable commercial value. CRISPR technology is a central technological development in this respect, being also the subject-matter of intensive patenting activity and patent-related disputes. Thomas Hedner and Jean Lycke explore the extensive technological potential of CRISPR innovations as well as the patent landscape in the field and discuss future trends in what may be expected to be a central area of future medicinal research.

Defining the concept of invention is without a doubt a challenge in the pharmaceutical sector. A new revolutionary invention might today consist of a new dosage regime or a second medical indication. Ester-Maria Elze discusses in her article how the novelty and inventive step requirement apply to dosage patents as well as the difficulties connected to their interpretation and enforcement on a national level. Claim drafting as well as enforcement of second medical indication patents are a complicated matter. Enforcement of second medical indication patents in Germany provides an interesting illustration of the difficulties of patent claim interpretation. As Clara Berrisch notes in her article, shaping the protection of second medical indication patents is still a work in progress.

John Hornby analyses UK case-law concerning the application of the Actavis equivalence test. He concludes that the balance has clearly been shifted in the UK in the direction of legal uncertainty. Parties and their advisors are being left to distil some generalized (though perhaps not amorphous) idea of what the extent of a patent's protection might be.

A major challenge of exercising exclusive rights in the pharmaceutical sector concerns how pharmaceuticals are sold. Applying for a patent is not the only nor the last thing a product owner has to do before placing the product on the market; pharmaceutical products need to successfully go through the stringent and time-consuming marketing authorization procedure. As a compensation for the time spent between the patent application and the actual commercialization date, the Supplementary Protection Certificate (SPC) Regulation provides an up to five-year exclusive right. The scope of this right and in particular the interpretation of article 3(a) of the SPC Regulation, and the definition of the term "product", are according to Lisa Åkerblom's article one of the most complicated aspects of the Regulation and the result of a "cultural shock" and a less successful transplantation from their American counterparts. The interface between patent rights and marketing authorization, in particular with respect to skinny labelling is also in focus in the recent CJEU case of Warner Lambert Company, analyzed in the case note by Sofia Bergenstråhle and Valter Gran.

The interplay between regulatory law and exclusive rights from an economic perspective is further explored by Ove Granstrand, who writes about the strategy of evergreening employed by pharmaceutical companies, with specific focus on the Losec case. Evergreening is generally the extension of the duration of an existing temporary monopolistic or market dominant position by various means or strategies.

The societal effects of patent protection of pharmaceutical products in particular on the international level are non-negligible. Katarina Foss-Solbrekk discusses how developing countries' access to medicines is impeded by the patent system as well as how flexibilities in the international and national legal framework contribute to this end. The article shows that while exceptions to patent rights might not be as effective, they have however triggered a very interesting development of voluntary licensing, a company-centered initiative providing access to free or low-priced pharmaceuticals. Thus, instead of addressing public health concerns by means of compulsory licensing and generic alternatives, the pharma industry itself takes the responsibility to provide pharma with affordable modern medicines.

Commercializing pharmaceutical products is of course not only about exclusive rights for the technology. Choosing an appropriate name for a new product is a daunting task. In other industries, this is usually left to the creativity of the marketing department but in the pharmaceutical industry there is a considerable regulatory framework to take into account. The practical implications of this framework and its limitations on creativity in pharma branding is analyzed in Kristina Björnerstedt and Gunnel Nilsson's article.

Chemical molecules, gene sequences, patient security, expensive and lengthy research, international markets, innovative business models and prioritized public health concerns constitute necessary ingredients influencing the way the IP system is applied and interpreted in the pharma sector. And it is this unique interaction that makes pharma so special.

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Evergreening and patent cliff hangers[1]

By Prof. Ove Granstrand, Chalmers Univ. (Dept of Mathematical Sciences)
and Cambridge Univ. (Centre for Technology Management)

1. PROBLEM BACKGROUND

1.1 A tragic windfall

The tragic 9/11 events in 2001 implied a delay in the court proceedings in Boston that dealt with a case involving AstraZeneca and its blockbuster drug Losec (Prilosec in the US). The key basic patent for this drug had been received by the Swedish company Astra in the US in 1981 (US patent # 4.255.431, issued March 10, 1981). Astra later merged with Zeneca in 1998-99, forming AstraZeneca ("AZ"). The delay in court proceedings in 2001, due to the unexpected and time-consuming involvement of the court in the 9/11 events, implied in turn that competitive entry of generica into the Losec market was also delayed. At this time media circulated an undemented estimate of 200 MUSD as the monthly profits reaped by AZ from this drug. These profits were to be heavily reduced by competitive entry which was sure to take place as soon as possible after the key patent expired, as generic drug manufacturers had prepared their "springboards" for entry into this lucrative market.

1.2 The patent cliff challenge

Right or wrong, the sales, profits and profit margin of a blockbuster drug are towards the end of its effective patent protection usually very large, which incentivizes pharma firms to employ a myriad of means/tactics/strategies to delay entries by competitors, i.e. means to maintain a competitive position and sustain any temporary competitive advantages, such as patent protection. The consequences of the expiration of a key patent in form of risks of a substantial drop in sales, profits and profit margins due to competitive entry, are particularly pronounced in the pharma industry in which non-intellectual property ("IP") based entry barriers are relatively difficult to erect during the effective patent protection. These drastic consequences of patent expiration are often referred to as "the patent cliff". In the case of AZ and its pre-merger constituent Astra, expiration of its key Losec patent, together with Astra's anticipated over-dependence upon Losec had early on been perceived as having such drastic consequences on its financial performance that it became an argument in favor of Astra's merger with Zeneca in 1998-99. Astra had since the 1980s tried to generate more radical innovations in its research and development ("R&D") pipeline but essentially without enough successes to be perceived as providing a business portfolio sufficiently diversified to pick up the company's expected financial drop from the patent cliff, perceived by some as suicidal while disputed by others.

1.3 The evergreening approach

Thus, all in all, extending the effective patent protection of Losec and its successor Nexium in a second product generation, i.e. what is referred to as evergreening, bridging the patent cliff had become a strategic issue for AZ with powerful incentives to invent various strategies to that effect.

AZ is not a unique case in this respect and many firms engage in various forms of evergreening. This is troublesome for competitors, not the least manufacturers of generic drugs in the pharmaceutical industry, who try to invent counterstrategies. Evergreening is also troublesome at an IP policy level since the statutory duration of intellectual property rights ("IPRs"), being a key policy variable for fostering dynamic competition, is in effect circumvented or invented around strategically by IPR users. Evergreening is finally troublesome for all agents on the purchasing and using side along with price regulating and anti-competitive agencies and since evergreening typically sustains high price levels. Pricing of pharmaceuticals is as complex as it is controversial and evergreening plays an important role in that context at the same time as it arguably plays an important role for managing patent expirations and financing continued R&D on the innovator side. How to trade-off the interests of innovative and imitative producers, users and society via the IPR-system is without doubt a problem, enlarged by the large values involved for all stakeholders as will be shown below.[2]

1.4 The Losec case

The paper presents in some detail the empirical case of the pharmaceutical blockbuster drug Losec, which was succeeded by the drug Nexium as a second product generation.[3] This case is particularly rich in many aspects of evergreening based on a dynamically extended portfolio of IPRs, patents and follow up patenting in particular, but also trademarks and trade dress, within and across two product generations, complemented by a successful global patent litigation strategy. The case, moreover, illustrates how a couple of IP policy developments substantially aided evergreening. In addition, it contains some unexpected drama, which is useful in getting attention to the evergreening phenomenon. The paper ends with a discussion of implications of evergreening strategies for managerial counter-strategies as well as for innovation and IP policies.

2. EVERGREENING DEFINED AND DESCRIBED

2.1 Evergreening defined

Evergreening in a general sense refers to the extension of the duration of an existing temporary monopolistic or market dominant position by various means or strategies. We can then talk more specifically about evergreening of sales or profits from products, technologies, services and equity. Evergreening can be accomplished by erecting entry barriers of all sorts and employing entry deterrence strategies for delaying entries or weakening competition and/or strengthening own competitive advantages when the dominant position is threatened. It is moreover a standard result in industrial organization theory that a monopolist has more to lose by the entry of a second company than the latter has to gain, something that incentivizes the monopolist to pay the prospective entrant for not entering, i.e. to engage in a so called reverse settlement or "pay for delay" scheme.[4] Typically evergreening has been practiced in the pharmaceutical industry when an IP-based temporary monopoly is about to expire, and then IP strategies for evergreening of IP as well as other means have been used to evergreen product sales.

2.2 How evergreening is used

This paper aims to explore the phenomenon of evergreening by means of IP strategies in general, and patent strategies in particular. If, e.g., an innovation through widespread adoption and diffusion has led to a high growth rate in a market with a low rate of technological substitutions, high switching costs and steep learning curves, then any prolongation of a dominant market position pays off handsomely. Traditionally evergreening involves follow-up patenting of product and process improvements and new and non-obvious applications or medical indications of the basic invention as illustrated in Figure 1.[5]

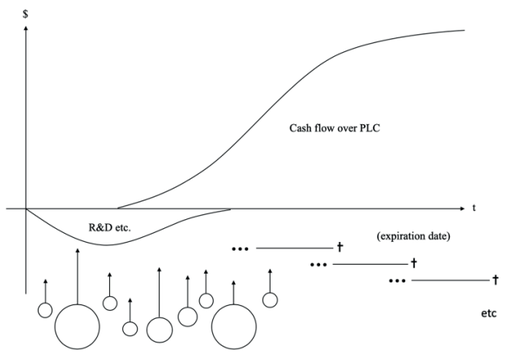

Figure 1 Continuous patenting and build-up of patent portfolio over time
Source: Granstrand (1999)

[1] Helpful comments on the paper and the topic have been received from Marcus Holgersson, Ivan Hjertman, Mike Scherer and Frank Tietze. The financial support from Vinnova under grant 2017-04469 for the project "Intellectual assets, innovation, growth and value creation and the role of new digital technologies and digital property" and the assistance of Andreas Opedal is gratefully acknowledged.

[2] See e.g. Feldman, R. (2019). Drugs, Money, and Secret Handshakes: The Unstoppable Growth of Prescription Drug Prices. Cambridge University Press, UK, for a recent study of pharmaceutical pricing in the US, and Scherer, F.M. (2004). The Pharmaceutical Industry – Prices and Progress. New England Journal of Medicine, 351(9), 927-32, for an international study.

[3] For further readings on the case, see Östholm, I. (1995). Drug Discovery – a pharmacists story. Swedish Pharmaceutical Press, Stockholm, Sweden; Sundling, S. (2003). Per aspera ad astra. Ekerlids; Granstrand, O., and Tietze, F. (2016). IP Strategies for Evergreening Inventions (CIM Working Paper 2016:1). Chalmers University of Technology, and Granstrand, O. (2018a). Evolving Properties of Intellectual Capitalism: Patents and Innovations for Growth and Welfare. Edward Elgar Publ., Cheltenham, UK.

[4] See a standard textbook like Scherer, F.M. (1980). Industrial Market Structure and Economic Performance (2nd rev. ed.). Chicago, IL: Rand McNally, or Tirole, J. (1988). The Theory of Industrial Organization. Cambridge, MA: The MIT Press.

[5] For a thorough study of legal aspects of pharmaceutical patents, see Domeij, B. (2000). Pharmaceutical Patents in Europe. Kluwer Law International. See also Domeij, B. (2003). Initial and follow-up pharmaceutical inventions in Europe. Published as Ch. 8 in Granstrand (2003), pp. 177-197, for some legal aspects of initial and follow-on pharmaceutical inventions.

Evergreening could also be accomplished by launching a series of product generations with overlapping technology or resource bases, where a strong patent position in the technological overlap is leveraged to a strong market position for the subsequent product generation as illustrated in Figure 2.

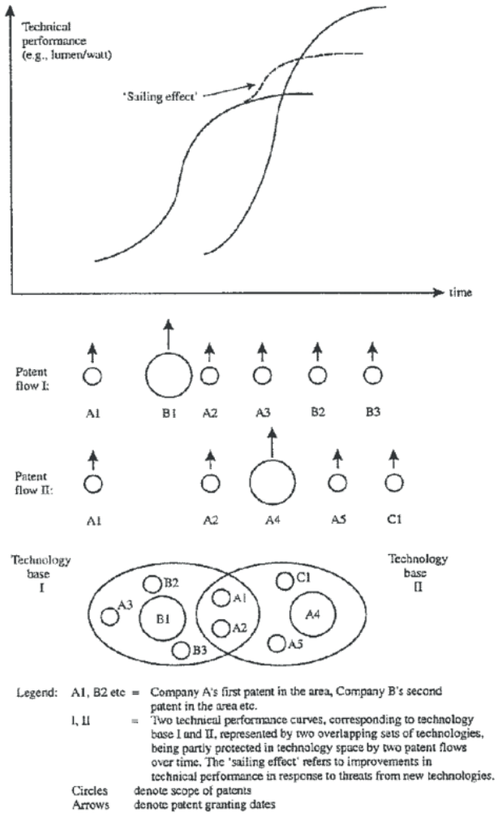

Figure 2 Patenting strategies in the case of two sequential product innovations (adapted from Granstrand, 1999)

Evergreening is well recognized in industry, especially in the pharmaceutical industry, and in some policy circles but it is not well researched by academia.[6] Firms are clearly incentivized to engage in evergreening, while the patent system is designed to encourage dynamic competition and the provision of innovations by granting innovators legal rights for achieving a temporary or time limited monopolistic position just long enough for innovators to recover their investments. In return for these rights innovators have to provide sufficient disclosure of their invention secrets to enable competitors to enter the market after patent expiration. However, such an institutional design carries the seeds to counter its purpose when the time limits are not set right or could be strategically surpassed by its users, incentivizing them to become abusers. Policy responses are then called for, but as the paper will show such a call and response is difficult to get in tune.

3. EMPIRICAL CASE[7]

3.1 Point of departure

The medical drug Losec (with generic name omeprazole) for stomach ulcers was developed at Astra-Hässle in Mölndal, Sweden, and launched with its first year of sales in 1988. It quickly became a commercial success and for several years was the world's annually best-selling drug. The basic patent on the active substance was applied for in 1978 in Sweden and in 1979 in Europe and the US, among other countries, and was granted in 1981 in the US – which meant that its validity in the US would expire in 1999 (although subsequently prolonged for 3 years). The basic patent can be regarded as a very strong one with a substantial inventive step and strategic blocking effect in terms of restricting possibilities for inventing around. Losec represented a whole new biological mechanism based on proton pump inhibitors and was thus a technologically radical innovation that also became economically very large since it attained huge growth and profitability. (The patent's past and future value was estimated by Astra-Hässle management in 2000 to lie between 15–30 billion US dollars (BUSD).)

This innovation contributed more than any other of Astra's radical innovations to making Astra one of the 15 largest global pharmaceutical companies, from having been among the 40 largest before Losec. As mentioned, in 1999 Astra merged with Zeneca to become AstraZeneca (AZ). A major motivation behind this merger was to create economies of scale and diversify the risks and vulnerability to the "patent cliff" impact upon profits and growth, i.e. the reduction in profits and sales due to patent expiration. Thus, major patents may have dual impact upon growth over time, possibly even leading to M&As. In 2004, AZ was the sixth largest pharmaceutical company and had sales of prescription drugs amounting to 21.4 BUSD, ranked after Merck and before Novartis.

Losec was further developed after its initial launch to include, for instance, an improved form of encapsulation for the active substance, which yielded a so-called formulation patent. This type of patent, although essential, did not have the same high inventiveness as the original substance patent but nevertheless required substantial R&D efforts and ingenuity. An essential step in the commercialization of Losec was precisely the development of a well-functioning pharmaceutical preparation. Astra sought and was granted a patent on the preparation, which proved to be very valuable in the competition with generic drug companies, i.e. companies that sell generic drug copies of an original drug, which typically then has lost its patent protection. An extra month without competition from generic drugs was said in the media to be worth at least 200 million US dollars for Astra.

Astra and later AZ was also forced to defend its patents in numerous court disputes in various countries. In the US, Astra very likely benefited from the greater propensity of US courts since the 1980s not to invalidate a patent under attack.

The case of Losec thus illustrates how strongly complementary patents with both large and small inventive steps altogether contributed to an enormous growth in value but also to risks of falling profits and growth after patent expiration. The drug Nexium, a descendant of Losec forming a second product generation, further illustrates the economic importance of more – in technical and scientific terms – modest progress and incremental improvement work along a science and technology trajectory. These cases demonstrate the important interplay and synergies between radical and more incremental product as well as process innovations. Figure 3 shows the sales pattern of the two product generations.

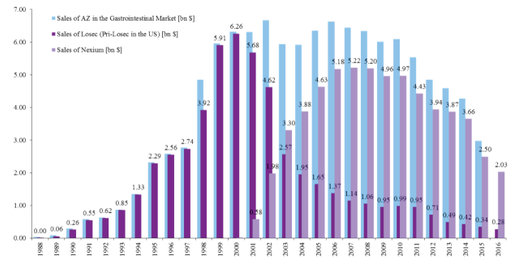

Figure 3 Evergreening of Losec by Nexium[8] (Source: Granstrand and Tietze (2016) and AZ annual reports)

3.2 IP value distribution

Table 1 shows how the value derived from IP is shared between the innovative producer, thought of as AZ, and consumers in different appropriation regimes. The underlying model is linear as a first approximation, and static as reflecting a year at the mature end of patent protected phase of the Losec product cycle, before the onset of generica and before the cannibalization of the second generation Nexium.[9] The assumptions of the model are of course disputable as well as the data, but still offer a ballpark estimate and some interesting interpretations.[10] First the value transfer from the innovator to consumers (without regard for equity) from competitive entry, or alternatively from hypothetical non-profit regulation, is indeed considerable and a good illustration of the patent cliff, a transfer that easily motivates extreme adversarial responses from all sides, and especially for the single "patent cliff hanger". Second, a hypothetical price regulation based on a fairness principle stipulating equal value sharing between innovator and users (intermediaries apart), actually reduces the monopolistic innovator's annual value capture only by 12.5%, while increasing the consumer value with 75%. This is quite surprising and constitutes food for thought about how to smooth a patent cliff through licensing on some fair terms, i.e. fair, reasonable and non-discriminatory terms ("FRAND") based licensing, which could be compulsory or even voluntary towards the approach of the patent cliff, rather than, say, a patent term restoration. Third, the absolute figures are large and uncertain but in line with the total value of the Losec strategic (=unavoidable) patent as estimated to be in the range of 25-50 BUSD.

Table 1 IP value distribution under different pricing regimes in BUSD per year[1]

Pricing	Consumer value	Producer value	Societal value
Monopolistic[2]	1.2	2.4	3.6
Competitive[3]	4.8	0	4.8
Regulated[4] for non-profit	4.8	0	4.8
Fair[5]	2.1	2.1 (=8/9 * 2.4)	4.2

Notes:
1) Case of radical product innovation with approximate linear demand and supply curves with constant marginal cost, constant dollars, and no discounting (since impact is per year). Fixed costs are partly sunk, partly variable costs. Value = surplus and societal value = welfare = consumer value + producer value (i.e. with no equity).
2) As a result of IP-based evergreening.
3) As a result of IPR expiration, and competitive market entry of generica.
4) As a result of non-profit regulation ("No profits in the welfare sector").
5) As a result of compulsory FRAND-based licensing, equalizing consumer value (surplus) and producer-value (surplus).

6 See Granstrand, O., and Tietze, F. (2016). IP Strategies for Evergreening Inventions (CIM Working Paper 2016:1). Chalmers University of Technology, for a survey of literature on evergreening.

7 This section draws on Granstrand, O. (2018a). Evolving Properties of Intellectual Capitalism: Patents and Innovations for Growth and Welfare. Edward Elgar Publ., Cheltenham, UK.

8 Note: AZ does not report cumulative figures for sales in gastrointestinal market for 2016.

9 The underlying model is outlined in Granstrand, O. (2018a). Evolving Properties of Intellectual Capitalism: Patents and Innovations for Growth and Welfare. Edward Elgar Publ., Cheltenham, UK, pp. 186-7.

10 A similar analysis with a linear demand curve is presented in Romer, P.M. (2002). When should we use intellectual property rights? American Economic Review, 92(2), 213-216, in the case of value sharing of copyrighted material through file sharing of music. Romer's analysis challenges the traditional design of copyright from an economic welfare analysis point of view, demonstrating the considerable net welfare gains from filesharing, despite its presumed negative effects upon value creation from production of new music.

4. DISCUSSION

4.1. Typologizing evergreening

From the case study we can distinguish between the following types of evergreening.

First, evergreening of a dominant market position on the product/technology/service/equity market can be accomplished by IP-based as well as non-IP-based strategies (e.g. reverse settlements, which was also used by AZ).

Second, IP-based evergreening strategies may in turn be based on single or multiple IPRs of a single IPR type or of multiple types of IPRs, i.e. through multi-protection. IPRs, and patents in particular, may then cover different features of products, processes, components (hard and soft), complementary products or devices, and applications. As for patents, they could be complementary as well as substitutes, e.g. for building patent fences or surrounding basic patents with application patents.

Third, although the case illustrates evergreening from the point of view of a single firm, multiple firms or organizational entities could engage jointly in evergreening.[11]

Figure 4 illustrates the duration of various major types of IPRs. Here it is interesting to note the conceivable impact of new technologies like artificial intelligence ("AI") and blockchain. AI based generation of patents, designs, copyrighted material and trademarks, passing a kind of Turing test (meaning that a patent and trademark office examiner cannot discover that the creation and rights application is computer generated) is likely to enhance the possibilities of evergreening, especially if the inventive step, originality or distinctive feature type of requirements are set low. As for database rights, granted on the basis of substantial and non-trivial investment in the database as has been the case in the EU, sensors and AI in Internet of Things systems certainly will facilitate evergreening.[12] In regards to trade secrecy, it will be enhanced by blockchain and encryption technologies. Thus enhanced technology based protection of IP will increase, which calls into question whether the IP protection by legal means has to be modified and rebalanced.

Third, evergreening may be intragenerational and intergenerational as illustrated by Losec and Nexium. The case of inter-generational evergreening or multi-generational evergreening with three product generations may be illustrated as in Figure 5 below.[13]

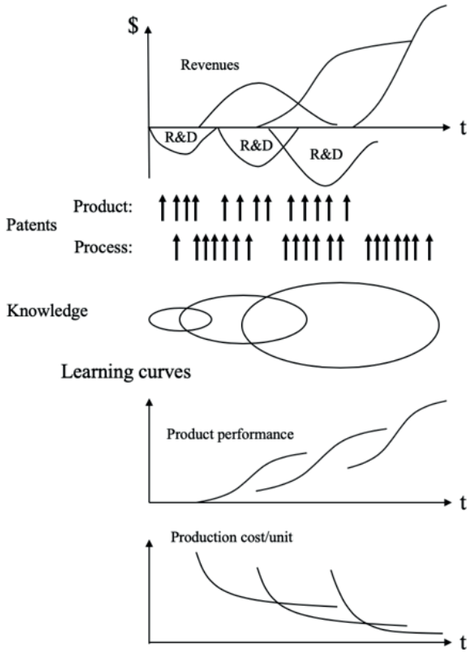

Figure 5 Patent based multi-generational evergreening with three generations

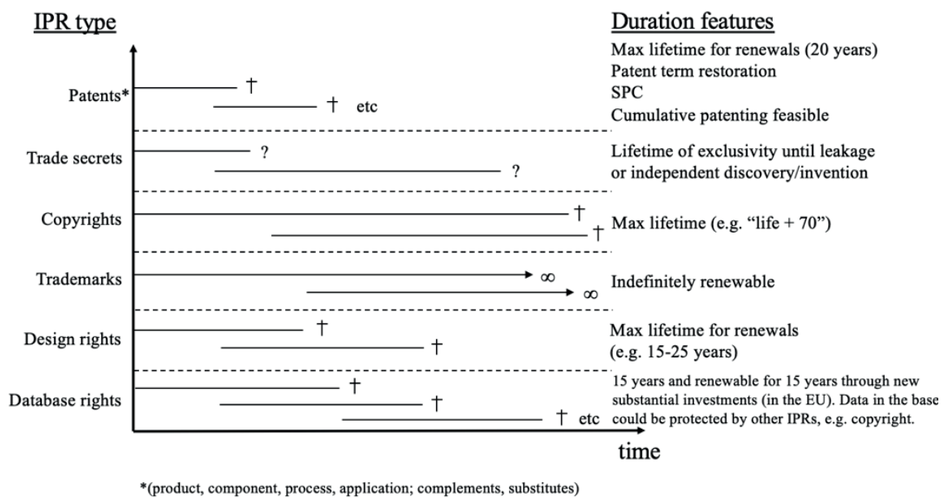

Figure 4 Evergreening features in multi-protection

4.2. The strategy-policy game

Many of the problems with the patent system derive from the fact that the system can be strategically gamed by its users in ways that are difficult to counter by policy makers, including law makers. This leads to a meta-game between strategists at industry level, who are involved in a competitive game with each other, and policy makers at the government level, who needless to say might be involved in games with each other as well. We will refer to this meta-game as the strategy-policy game.[14]

This kind of meta-game is more or less omnipresent in any decentralized governance system and it should come as no surprise that it is present in the patent system in general. Evergreening by exploiting the rules in the patent system then provides a good illustration of the strategy-policy game as strategists want to increase the duration of effective patent protection in order to increase monopolistic rents while policy makers want to limit it in order to increase competition. At the same time, viewing evergreening as a strategy-policy game provides useful analytical tools for coping with evergreening. One such tool is a strategy-policy matrix as shown in Table 1, considering the categories of policy-makers (without a competing category), evergreeners and their competitors.

As seen from Table 1 there are many elaborate strategy options for evergreening and a fair amount of response strategies, while the standard patent policy variables are relatively few, i.e. duration, inventive step (non-obviousness), scope of protection, patentable subject matter and patenting fees. It is outside the scope of this exploratory paper to make an economic policy analysis of evergreening and suggest policies to cope with it, but a few observations and reflections are in order. First, it is a daunting task to assess the economic consequences of evergreening that operates in increasingly complex technologies with significant prospects as well as costs for improvements with unclear counterfactuals. Evergreening defendants may argue somewhat in line with Kitch's prospect theory and the standard critique of that theory is difficult to empirically verify.[15] Nevertheless, evergreening is widespread and probably increasingly so and it runs counter to the basic idea of limiting the duration of IPRs, patents in particular. This clearly calls for policy analysis and research, which in turn requires clear definitions, operationalizations and typologies, to which end this paper hopefully has made some contributions. Second, even if evergreening is found to be detrimental to innovativeness, growth and welfare, at least certain types of it, it is difficult to find effective policy remedies that can add to the countering effects of strategies against it, i.e. add to the market forces.[16] This is so much due to the compounded effects of changes in terms of the parameters or policy variables in the patent system with its one-size-fits-all features and the industry specific nature of evergreening. More restrictions on the use of patent term restorations upon application are possible.

[11] An example is the Microsoft-Intel alliance with the so called Wintel combination of software and hardware platforms.

[12] For a good review of the legal protection of databases in the EU, see Axhamn, J. (2016). Databasskydd. Stockholm University.

[13] A good case of multigenerational evergreening is the Gillette sequence of razors with 1-2-3-4-5 razor blades, each number of blades defining a product generation covered by numerous patents of which some read on more than one generation. The use of backward and forward compatibility of razors and razor blades and standards further contributes to evergreening.

[14] This type of game can be looked upon as being played in simple cases at two levels with two competing categories of collaborating players at each level – a rule-making level and a subordinate rule-playing level.

[15] See Kitch, E.W. (1977). The Nature and Function of the Patent System. Journal of Law and Economics, 20(2), 265-290, for the theory and Kaufer, E. (1989). The economics of the patent system. Chur: Harwood Academic Publishers, for the critique of it.

[16] The Federal Trade Commission (FTC) in the US has voiced concerns, emanating in a legal brief in a special case in 2012, that reformulations of a pharmaceutical, dubbed a "product hopping" strategy by the FTC, in effect can be detrimental to competition by helping to keep generics out of the market rather than providing useful medical innovations (The Economist, June 21st 2014, p.72).

Table 2 The strategy-policy matrix for patent based evergreening[17]

EVERGREENING STRATEGIES

For	Against[18]
• Search and research for strategic patents and patent fences • Fragmentation and patenting of complementary resources and elements in the business innovation system, typically by • Follow-on/continuous sequential patenting of product/process improvements, features and applications for the innovation and its related complements • Aggregation and patenting of substitute resources and products/ technologies, typically by blocking patents and patent fencing outside the own product area (cf "offensive patenting"[19]) • Sequential patent blanketing and patent flooding • Multi protection, combining patents with other IPRs • Grant-back licensing • Deterring litigation and litigation threats, possibly using NPEs (non-practicing entity) and privateering[20] • Lobbying	• Invalidation[21] • Invent around • Patent or license acquisition • Patent pooling and cross-licensing • Partnering • Use of general bargaining power, e g purchasing or procurement power • Ignore and/or infringe • Delay entry until patent expiration • Abandon entry and related commercial operations and R&D • Patent racing to foreclose evergreening patents, e g by surrounding a strategic patent with application patents or invent around or racing for strategic improvement patents.

EVERGREENING POLICIES

For[22]	Against
• Patent term restoration • Injunctions • Delaying licenses, concessions, approvals, litigation etc.	• Reduction of statutory duration • Reducing the scope of protection • Reducing patentable subject matter • Increasing the inventive step requirement • Increasing patenting fees for sequential and/or substitute patents • Market power abuse intervention • Compulsory licensing • Abandoning the patent system

Raising the inventive step requirement is also possible but with mixed effects upon evergreening since possibilities to patent minor sequential improvements are reduced but so are invent around possibilities.[23] Third, policy remedies are perhaps more called for and also more easy to find for some other forms of evergreening, not being based on patents, as practiced in the pharmaceutical industry (including AZ in the Nexium case), reverse settlements and branding post-patent drugs. The latter form of evergreening is based on IPRs, trade marks in particular, and could be surprisingly effective and profitable, not the least in countries with generics of poor quality, a fair amount of corruption, weak government price controls and a foreign-is-better syndrome among buyers, prescribers and users, promoted by various means by foreign producers.

[17] The table gives important and common examples of patent-based evergreening but is not exhaustive. Non-patent based means for evergreening of product sales also exist such as marketing of branded products after patent protection has expired ("off-patent" products) and reverse settlements ("pay-for-delay" of entry).
Moreover, policies as well as strategies for and against evergreening could be regarded as opposites and included in the matrix as such. Similarly policies aimed at strengthening or weakening the propensity to employ a certain strategy could be included. Such examples that are easy to derive logically are excluded here, however.

[18] Response strategies to blocking patents in general apply here, see Granstrand, O. (1999). The Economics and Management of Intellectual Property: Towards Intellectual Capitalism. Cheltenham, UK and Northampton, MA, USA: Edward Elgar Publishing, pp.232-234 in addition to patent strategies to foreclose evergreening patents.

[19] The dichotomy defensive/offensive patenting is avoided here since it is both unclear and value-laden.

[20] See especially Ewing, T.L. (2011). Indirect Exploitation of Intellectual Property Rights by Corporations and Investors: IP Privateering & Modern Letters of Marque & Reprisal. Gothenburg: Chalmers University of Technology, on privateering. The use of privateering specifically for evergreening is likely although unclear, however.

[21] Invalidation of patents, especially by digging up prior art, is more common than generally recognized and could possibly affect a major share of all patents, see in particular Henkel, J., Schöberl, S., and Alexy, O. (2014). The emergence of openness: How and why firms adopt selective revealing in open innovation. Research Policy, 43, 879-890.

[22] Policies are taken in a broad sense here and includes laws, regulations, agency decisions and interventions. Policies in a narrow sense explicitly designed to promote evergreening in general are fairly rare in practice as to be expected. In theory they are conceivable, however, e g in line with the arguments in Kitch's prospect theory, claiming that a broad and durable protective scope in emerging technologies allows for more coordinated subsequent improvement processes by the rights holder.

[23] Raising the inventive step requirement could be justified on other grounds such as the need to reduce transaction costs, see Granstrand, O. (ed.) (2003). Economics, Law and Intellectual Property. Boston, MA: Springer, Ch 10 for an empirical and theoretical study with this conclusion.

[24] For derivation details, see Granstrand, O. (2018b). Industrial Innovation Economics and Intellectual Property (7th ed.). Gothenburg, Sweden: Svenska Kulturkompaniet, pp. 185-6.

APPENDIX

Some simple pricing models for radical product innovations

Assuming the radical product innovation has created a new market which in a given period in a mature stage has a linear demand curve with price p and quantity q, constant marginal cost c and fixed investment cost FC, elementary micro-economic theory tells us that the optimal profit maximizing price p_m for a monopolistic innovation is the average of the maximal willingness to pay among customers b and the marginal cost c, i.e.

$$p_m=(b+c)/2$$

which gives the innovator the maximal profits

$$\tilde{\pi}_m=(b-c)^2/4a-FC$$

Competitive entry and perfect competition on the other hand as the opposite extreme (and thus idealized case) gives the competitive market price

$$p_c=c$$

and zero surplus profits (above variable costs, including cost of capital) for competitors and thus no contribution to any fixed costs. A price regulator that wants to set a price p_r that eliminates the innovator's surplus profits, taking fixed costs into account, and maximizes welfare (as the sum of consumer surplus value and producer surplus profits):

$$p_r=p_m-\sqrt{a\tilde{\pi}_m}$$

A price p_f, regulated or negotiated, which is fair in the sense that it equalizes aggregate consumer value created by the innovation and the innovator's profits, then is:

$$p_f=(b+2c)/3$$

which gives the innovator profits

$$\pi_f(p_f)=2(b-c)^2/9a-FC$$

Thus, a monopolistic innovator would lose

$$\pi(p_m)-\pi(p_f)=(b-c)^2/36a$$

by fair pricing.[24] Whether this fair pricing is reasonable in some sense is left as an open question.

Ove Granstrand

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CRISPR/Cas9 system and gene editing tools – On patent rights, recent disputes and its potential commercial applicability in biotechnology and medicine

By Thomas Hedner and Jean Lycke

ABSTRACT

The CRISPR/Cas9 discovery has emerged as a powerful technology tool to edit genomes, which allows researchers, innovators and life science entrepreneurs to alter DNA sequences and modify gene function in a range of species. The simplicity, high efficiency and seemingly broad use of the CRISPR/Cas9 system has led to hopes that this disruptive technology may have the potential to transform important sectors of biotechnology and medicine. The technology will enable users to make changes in the sequence or expression of virtually any gene, cell type or organism. The rapid progress in the development of CRISPR/Cas9-based technologies over the past years has been extraordinary. In spite of that, many outstanding questions remain to be addressed, and potentially interesting applications as well as potential risks yet need to be explored. Without doubt, the rapid advances and extensive commercial applicability of the CRISPR technologies is likely to a have a societal impact within the decades to come.

In medicine, recent and future advances in the applicability of Cas9-based systems for genome and epigenome editing are likely to advance the technology forward to therapeutic applications, in respect to treatment of a variety of human diseases. In biotechnology, these techniques may be exploited in several respects to the benefit of society at large. In the biosciences, the CRISPR technology may have significant applications to make changes in the genome of various forms of organisms, including cells of domestic animals, cells of plants and various crops, bacteria, viruses and other cells. The technology may also find a future use in "de-extinction" of various animals such as the woolly mammoth and passenger pigeon.

The recent discoveries and developments have led to extensive patenting efforts, resulting in some major patent disputes. The extensive patenting may risk creating a scenario, which could hamper the further development of this technology and ultimately limit full value creation of this technology for major societal and industrial stakeholders.

1. INTRODUCTION

The CRISPR technology, which allows researchers to easily alter DNA sequences and modify gene function has over the past decade emerged a simple and powerful tool for editing genomes[1] The CRISPR/Cas9 is a system initially found in bacteria as a mechanism involved in immune defence. Bacteria use CRISPR/Cas9 to cut up the DNA of invading viruses to avoid being killed by the virus invasion. From its initial discovery, scientists have adapted this bacterial molecular machinery for entirely different purposes. Molecular engineering has made it possible to use this system to change any chosen nucleotide (or "letter") in the DNA code of an organism. By doing so, CRISPR/Cas9 can be used to correct a disease-causing genetic error that was inherited or occurred later in an individual´s DNA when replicated. Alternative uses of the technology may be to change the genetic code in order to enhance or introduce specific functions in e.g. plants to improve crops or to modify genes in domestic animals. There are also on-going efforts to bring back extinct species to life that were previously eradicated by humans.[2] However, in addition to the wide range of possible favourable applications of the CRISPR/Cas9 technology, the technology also raises a range of ethical concerns.[3]

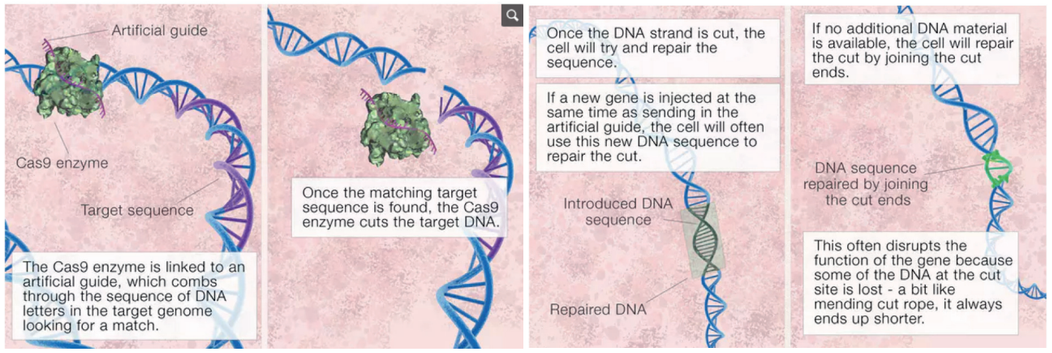

Figure 1: CRISPR/Cas9 technologies may be used as DNA editing tools in medicine and biotechnology. The Cas9 "scissors" is provided with a copy of the DNA to be altered in order to identify where to cut the DNA strand. If a selected new DNA strand is injected, it will take the place of the DNA that was cut out.

Cas9 is the technical name for the virus-destroying "scissor" protein that evolved in bacteria. The CRISPR part of the acronym relates to the specific DNA sequences of the complex immune system telling the Cas9 "scissors" where to cut the DNA strand (see Figure 1). CRISPR is an abbreviation for *"Clusters of Regularly Interspaced Short Palindromic Repeats."* The term refers to a specialized region of DNA, presenting with nucleotide repeats and spacers. Such repeated nucleotide sequences, (DNA building blocks) are distributed throughout a CRISPR region.[4] Spacers are pieces of DNA, which are found interspersed among the repeated sequences. The CRISPR systems initially identified in bacteria, as adaptable and dynamic immune mechanisms, which the bacteria had developed in order to protect themselves from alien virus or plasmid nucleic acid material.[5]

In order to modify the genetic code (see Figure 1), a unique DNA sequence guide code can be made that will line up with only one specific part of the 3 billion base pair long genome in the cell. By carefully designing the DNA sequence, only one section of the DNA will match it exactly. After administration, the new DNA sequence will then move around in the cell and move into the only place where it fits among the billions of pieces of base pairs in the genome. In practice, the CRISPR/Cas9 components are administered together with the donor DNA to alter the gene. In the laboratory, it can be made by simple injection, or by a range of other molecular biology techniques. Importantly, in real life, it is also possible to administer the essential CRISPR/Cas9 components directly to living humans or animals. Taken together, with the CRISPR/Cas9 technology it is easy to change the genome of any form of life, by cutting away genes, or inserting new genes.[6]

In this review, we provide an overview of how this CRISPR/Cas9 system works and how it has been applied to perform genome editing across a wide variety of cell types and whole organisms. We also discuss the current extensive patenting efforts from many different actors. Further we describe the recent and on-going patent disputes following the discovery and early exploitation of this system. Finally, we speculate on future challenges related to commercial exploitation that needs to be addressed for efficient use of this emerging genome editing platform in clinical medicine and diverse areas of biotechnology.

2. CRISPR/CAS 9 – A BREAK-THROUGH DISCOVERY

CRISPR/Cas9 is a type of molecular machinery found in some bacteria, including *Streptococcus pyogenes*. The task of this machinery is to destroy intruding DNA chains, originating for example from attacking viruses.[7] A major leap towards this break-through technology was made by Emmanuelle Charpentier when studying the immune system of bacteria, during a visiting professorship at the University of Umeå in Northern Sweden. It was previously known that bacteria have their own kind of "vaccination program" that protects against attacking viruses, which was known as CRISPR/Cas9. When Emmanuelle Charpentier and her colleague Jennifer Doudna studied this system, they discovered how to control this bacterial defence system, and use it to cut and paste the genome of virtually any cell of interest.[8]

1 Lander, E.S. (2016).The Heroes of CRISPR, Cell January 14, 2016 , Crossley, M, (2018). What is CRISPR gene editing, and how does it work? The Conversation, January 31, 2018. https://theconversation.com/what-is-crispr-gene-editing-and-how-does-it-work-84591 and Vidyasagar, A. (2018). What Is CRISPR? Live Science April 20, https://www.livescience.com/58790-crispr-explained.html.

2 Crossley, M., (2018). What is CRISPR gene editing, and how does it work? The Conversation, January 31, 2018. https://theconversation.com/what-is-crispr-gene-editing-and-how-does-it-work-84591

3 Vidyasagar, A. (2018). What Is CRISPR? Live Science April 20, https://www.livescience.com/58790-crispr-explained.html.

4 Ibid.

5 Sander, J.D. & Joung, J.K. (2014) CRISPR-Cas systems for genome editing, regulation and targeting. Nat Biotechnol. 2014 Apr; 32(4): 347–355. doi: 10.1038/nbt.2842.

6 Ishino Y., Mart Krupovic, M., Forterrea, P. (2018). History of CRISPR/Cas from encounter with a mysterious repeated sequence to genome editing technology. J Bacteriology April ,200 (7),: 1-17, e00580-17.

7 Crossley, M. (2018). What is CRISPR gene editing, and how does it work? The Conversation, January 31, 2018. https://theconversation.com/what-is-crispr-gene-editing-and-how-does-it-work-84591.

8 Doudna, A. & Charpentier, E. (2014). The new frontier of genome engineering with CRISPR/Cas9. Science 28 Nov: 346 (6213) doi: 10.1126/science.1258096,

The machinery has two main components. One is a protein, Cas9, which is an enzyme that cuts DNA chains. The other is a collection of DNA fragments, called CRISPRs (Figure 1).

Cas 9: This enzyme extracts a DNA fragment from CRISPR and searches for occurrences of the same sequence in other DNA chains. When Cas9 identifies such a DNA sequence, it cuts off this DNA chain, which then loses its ability to perform its function. In the bacteria, which are under attack, the spacer DNA pieces are taken from viruses that previously attacked the organism. These DNA fragments serve as a memory bank, which enables bacteria to recognize the viruses and defend them from future viral attacks. When the components of this natural defence system are introduced and put to work in more complex, organisms, it allows for the manipulation of genes, or "genetic editing" in various mammals or plant species.

CRISPR: The CRISPRs are specific strands of DNA, while the protein Cas9 (or "CRISPR-associated") is an enzyme capable of cutting strands of DNA, acting like a pair of "molecular scissors". The term "CRISPR" sometimes also stands for "CRISPR/Cas9." The CRISPR natural defence mechanisms of bacteria and archaea (the domain of single-celled microorganisms) have developed over evolution to fight off attacks by viruses and other foreign bodies. That system builds on CRISPR-derived RNA and various Cas proteins, including Cas9 (Figure 1), which allows the defending cells to cut and destroy the DNA from a foreign invader. The spacer is incorporated into the host DNA, and when the virus attacks the host cells again, a portion of the CRISPR DNA will be transcribed and processed into CRISPR RNA, or "crRNA." The nucleotide sequence of the CRISPR can then act as a template to produce a complementary sequence of single-stranded RNA (crRNA), consisting of a nucleotide repeat and a spacer portion.[9]

The Cas9 protein is essentially an enzyme that has the capacity to attack foreign DNA. The Cas9 protein then binds to two RNA molecules, one of which is crRNA and the other tracrRNA (or "trans-activating crRNA"). These two RNA molecules then guide Cas9 enzyme to the target site where it can cut the target DNA, which may be complementary to a 20-nucleotide stretch of the crRNA. The Cas9 can cut cuts both strands of the DNA double helix, and make a "double-stranded break".

The CRISPR/Cas9 system also has a built-in safety mechanism, which prevents Cas9 to just cut anywhere in a genome. This mechanism is made up of short DNA sequences called PAMs ("protospacer adjacent motifs"), which are located adjacent to the target DNA sequence and serve as "tags" for Cas9. If the Cas9 complex does not identify a PAM next to the target DNA sequence, it will not cut the DNA. This safety mechanism may be reason why Cas9 never attacks the CRISPR region in bacteria.[10]

Due to these functionalities, it is possible to use the CRISPR systems to do specific genomic sequence changes in living cells and organisms. CRISPR/Cas9 can therefore be used as a powerful tool not only in biological research, and it also has the potential system to be used in the management of specific forms of genetic diseases. Such targeted genome editing will provide a new method to induce targeted deletions, insertions or to make precise sequence changes in a broad range of biological organisms and cell types. For example, specific nucleotide sequence alterations can be made to correct defective genes for therapeutic applications in specific genetic diseases, or to transfer valuable traits to agricultural crops and livestock. Although the early work related to CRISPR/Cas9 gene-editing system began in the 1990s, the full identification and understanding of these mechanisms has stretched over decades.

In 2009 Emmanuelle Charpentier and her research group

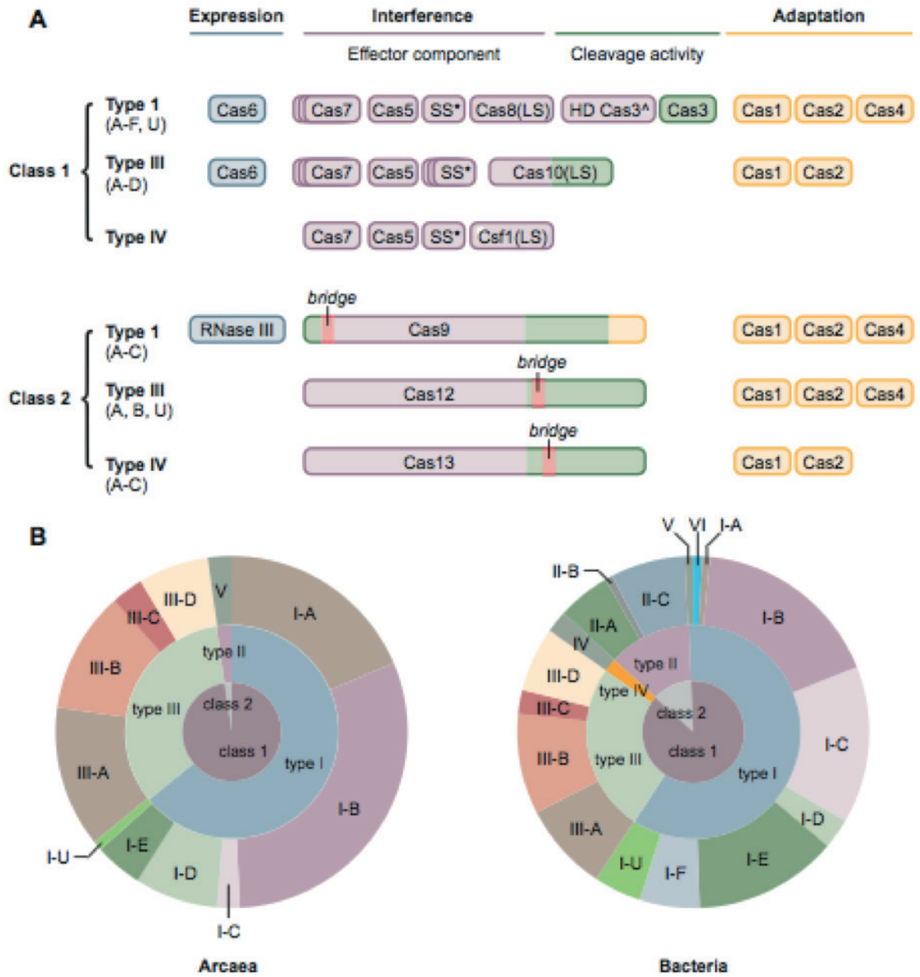

Figure 2: A recent overview and classification of CRISPR/Cas immune systems. Adapted from Ishino Y, Mart Krupovic M, Forterrea P. History of CRISPR/Cas from Encounter with a Mysterious Repeated Sequence to Genome Editing Technology. J Bacteriology April 2018 Volume 200 (7), pp 1-17, e00580-17 (see fn. 6)
A - upper panel. CRISPR-Cas classification into two major classes depending on whether the effector is a complex composed of multiple Cas proteins or a single effector. This is based on detailed sequence analyses and gene organization of the Cas proteins. In addition to The conventional types are I, II, and III, and in addition to that, types IV and V were added to classes 1 and 2, respectively. Types IV and V are those proteins which do not have Cas1 and Cas2, necessary for adaptation process, in the same CRISPR loci. The most recently added to class 2 was Type VI.
B - lower panel .This chart shows the proportions of identified CRISPR/Cas loci in the total genomes of bacteria and archaea from the current literature. Loci that could not be classified unambiguously were not included.

at Molecular Infection Medicine (MIMS) at Umeå University in Sweden had discovered how *Streptococcus pyogenes* used the enzyme Cas9 in its defence against virus attacks.[11] Key papers were published in the journals Nature 2011 and in Science 2012 by teams led by Emmanuelle Charpentier and Jennifer Doudna, showing that the natural machinery in a cell could be turned into a "programmable" editing tool, which could cut any DNA strand.[12] The follow-up research by Charpentier and Doudna, also enabled work on a modified and stabilized Cas9, which led to a series of advances in the use of the "genetic scissor" technology which is available today.[13]

The Cas9-based method has since 2012 been refined into a more precise and reliable technique to modify DNA strands in cell nuclei. The technology is today increasingly used by molecular biologists, to make changes in the genome of various forms of organisms, including mammalian cells, plant cells, and bacteria. During the years following the discovery by Charpentier and Doudna, scientists started to extend the gene editing efforts to the genomes of human cells. In January 2013, researchers from laboratories at Harvard and Broad Institute led by Feng Zhang were first to publish papers showing that this could be done.[14] Doudna also published results confirming this a few weeks later.[15] It then became clear to almost everyone in the field that CRISPR might become a flexible way to thera-

[9] Doudna, A. & Charpentier, E. (2014). The new frontier of genome engineering with CRISPR/Cas9. Science 28 Nov: 346 (6213) doi: 10.1126/science.1258096.

[10] Ibid.

[11] Deltcheva, E., Chylinski, K., Sharma, C.M., Gonzales, K., Chao, Y., Pirzada, Z.A., Eckert, M.R., Vogel, J. & Charpentier, E. (2011). CRISPR RNA maturation by trans-encoded small RNA and host factor RNase III. Nature 471; 602–607.

[12] Deltcheva, E., Chylinski, K., Sharma, C.M., Gonzales, K., Chao, Y., Pirzada, Z.A., Eckert, M.R., Vogel, J. & Charpentier, E. (2011). CRISPR RNA maturation by trans-encoded small RNA and host factor RNase III. Nature 471; 602–607 and Jinek, M., Chylinski, K., Fonfara, I., Hauer, M., Doudna, J.A., & Charpentier, E. (2012). A programmable dual-RNA–guided DNA endonuclease in adaptive bacterial immunity. Science. Aug 17; 337(6096): 816–821. doi: 10.1126/science.1225829.

[13] Charpentier, E. & Doudna. J.A. 2013. Biotechnology: Rewriting a genome. Nature 495(7439):50-51 and Doudna, A. & Charpentier, E. (2014). The new frontier of genome engineering with CRISPR/Cas9. Science 28 Nov: 346 (6213) doi: 10.1126/science.1258096.

[14] Cong, L., Ran, F.A., Cox, D., Lin, S., Barretto, R., Habib, N., Hsu, P.D., Wu, X., Jiang, W., Marraffini, L.A. & Zhang, F. (2013). Multiplex genome engineering using CRISPR/Cas systems . Science Feb 15; 339(6121): 819–823 doi: 10.1126/science.1231143 and Hsu, P.D., Lander, E.S., Zhang, F. (2014). Development and Applications of CRISPR/Cas9 for Genome Engineering (Review). Cell 157, (6) 5: 1262-1278, June 2014, https://doi.org/10.1016/j.cell.2014.05.010.

[15] Qi, L.S., Larson, M.H., Gilbert, L.A., Doudna, J.A., Weissman, J.S., Arkin, A.P., Lim, W.A. (2013). Repurposing CRISPR as an RNA-Guided Platform for Sequence-Specific Control of Gene Expression. Cell 152 (5), 1173-118, 28 February, doi.org/10.1016/j.cell.2013.02.022.

peutically modify DNA, and a tentative method to treat rare metabolic problems and genetic diseases in humans.[16] Such previously difficult to treat diseases ranged from blood disorders such as haemophilia to neurodegenerative diseases such as Huntington's.

The discovery of the CRISPR/Cas microbial adaptive immune system and its development into a gene editing tool represents the work of many scientists from various laboratories around the world. The timeline presented below (Table 1) provides a brief history of some of the major findings of the scientists who contributed to move this field forward. Such discoveries include the initial discovery of CRISPR and its function to the first demonstrations of CRISPR-mediated genome editing. For further details on the history of CRISPR research, see review by Lander.[17]

A number of methods to modify bacterial CRISPR/Cas systems have thus been developed into unique and flexible technological platforms. Any efforts to re-program a CRISPR editing system require identification and deletion of a particular piece of DNA. In practical terms, this requires only the synthesis of a custom RNA strand, which today can be done easily and cost-effectively. Researchers can simply order an optional RNA sequence online for delivery the next day or the same day, at a cost from a few to about a hundred USD. With the custom RNA sequence and a basic CRISPR kit, which is also inexpensive, an individual researcher can perform a gene-editing job quite easily.

TABLE 1
CRISPR/Cas9 discoveries and development timeline

Discovery of CRISPR and its function
1993 - 2005 — Francisco Mojica, University of Alicante, Spain

Discovery of Cas9 and PAM
May, 2005 — Alexander Bolotin, French National Institute for Agricultural Research (INRA)

Hypothetical scheme of adaptive immunity
March, 2006 — Eugene Koonin, US National Center for Biotechnology Information, NIH

Experimental demonstration of adaptive immunity
March, 2007 — Philippe Horvath, Danisco France

Spacer sequences can be transcribed into guide RNAs
August, 2008 — John van der Oost, University of Wageningen, Netherlands

CRISPR acts on DNA targets
December, 2008 — Luciano Marraffini and Erik Sontheimer, Northwestern University, Illinois, USA

Cas9 cleaves target DNA
December, 2010 — Sylvain Moineau, University of Laval, Quebec City, Canada

Discovery of tracrRNA for Cas9 system
March, 2011 — Emmanuelle Charpentier, Umea University, Sweden and University of Vienna, Austria. The final piece to the puzzle in the mechanism of natural CRISPR/Cas9-guided interference came from the group of Emmanuelle Charpentier

CRISPR systems can function heterologously in other species
July, 2011 — Virginijus Siksnys, Vilnius University, Lithuania

Biochemical characterization of Cas9-mediated cleavage
September, 2012 — Virginijus Siksnys, Vilnius University, Lithuania and
June, 2012 — Charpentier and Jennifer Doudna, University of California, Berkeley, USA

CRISPR/Cas9 harnessed for genome editing
January, 2013 — Feng Zhang, Broad Institute of MIT and Harvard, McGovern Institute for Brain Research at MIT, Massachusetts, USA

3. A RUSH TO PATENT

The CRISPR/Cas9 technology has been called the greatest discovery of the decade and some even call it the discovery of the century. The cellular CRISPR system, essentially represents a "search and replace function" for DNA, which allows disabled or dysfunctional genes may be replaced by new DNA letters in order to change or normalize their function. If, or rather when the CRISPR technology turns out to be a commercially important way to modify living cells, then the intellectual property and commercial control over the underlying key technological steps could be worth billions of USD in future revenues.

Today, the patent landscape related to CRISPR/Cas9 technology is becoming increasingly complex. For any party successful in claiming IP, there may be opportunities to claim rights to an innovation platform that may turn out be one of the most important genetic engineering techniques in recent biotechnology.[18] The technique has made it much easier to design potential cures to severe genetic diseases, eradicate pests, and to genetically modify plants. There are also attempts to genetically engineer pigs so that they can become suitable organ donors to humans, to name just a few examples. Anyone who holds this patent can engage in applications, which may have significant future value. Feng Zhang, Jennifer Doudna and Emmanuelle Charpentier have founded their own biotech companies, where venture capitalists have already invested several hundred million USD.

When various stakeholders early on became aware of the potential value of the CRISPR technologies, venture capital groups quickly began to recruit the key scientists, aiming to patent key steps in the CRISPR process and form gene-editing startups. Charpentier became associated with CRISPR Therapeutics in Europe. Doudna joined the company Caribou Biosciences, and in 2013 she joined Zhang and Church in the company Editas as a cofounder. Editas attracted a start-up capital of $43 million from some leading venture funds.[19]

Another important event took place in April of 2014, when Zhang and the Broad Institute was awarded the first of a series of US patents covering the use of the CRISPR technology in eukaryotes which essentially includes the use of the technology in any species whose cells contain a nucleus.[20] This included the rights to use CRISPR technology in mice, pigs, cattle, humans, or in every creature other than bacteria.

The approval of this patent surprised many of the stakeholders involved in the CRISPR race. To get the patent application reviewed quickly, Broad Institute had paid extra and along with the patent application came more than 1,000 pages of additional support documents. In less than six months, the application was approved by the USPTO, and few of the stakeholders knew it was underway. According to Broad Institute, the work of Doudna and Charpentier had only predicted that the technique could work in humans, and claimed that Zhang had made the discovery proving that the CRISPR technique would work in humans. Therefore, it was argued that Zhang was the first to show it, in a separate and "surprising" act of invention underlying the patent claim. The patent disclosure has caused considerable distress among researchers and start-ups. Several of those scientists claim that they also at an early stage managed to get CRISPR to work in human cells, a claim which also the scientific literature seems to support. This will be an important matter of discussion, since the easy reproducibility in different organisms is the most important hallmark of the CRISPR technology. Thus, many argue that, in patent terms, it was more or less "obvious" that CRISPR would work in human cells as well. If this is correct the invention claimed by Zhang and co-workers might not have the novelty, nor the inventive step/non-obviousness required to meet the requirements of patent protection.[21]

4. THE BROAD INSTITUTE VS BERKLEY CRISPR PATENT DISPUTE

Currently, only the first round has just been settled in the patent dispute for the new genetic CRISPR/Cas9 engineering technology. At stake is, not only potential future revenues of several billion USD, but also a likely Nobel Prize. Emmanuelle Charpentier and Jennifer Doudna are currently some of the hottest Nobel Prize candidates in Chemistry and/or Medicine. They have already received several major awards, including the Breakthrough prize 2015.[22] The US patent on CRISPR/Cas9 awarded to Zhang in 2014 could give him and his research centre control over the most important commercial uses of the technology on the US but probably not in all markets. The recent legal developments also imply that the commercial control of CRISPR/Cas9 patents might in fact end up in different hands. If not solved this will lead to a debate over who invented what, and when, and risk to create a legal controversy or a stalemate over actual ownership. Involved in such a battle are several heavily financed start-up companies, a half-dozen universities, and numerous legal advisors and other stake-holders.

Feng Zhang was also one of the first researchers to explore the CRISPR/Cas9 system and his research team was the first to succeed in modifying multicellular organisms with the new technology. Although he managed to receive a US patent for the technology, Charpentier and Doudna appealed the patent. From 2016 and on, the parties were negotiating with the US Patent and Trademark Office (USPTO) who was the rightful owner of the discovery itself. It is big money at stake, and behind Jennifer Doudna stands Berkeley University on the US West Coast and behind Feng Zhang stands the Broad Institute, an academic institution founded by the top universities MIT and Harvard, on the US East coast.

16 Xu, X., Qi, L.S. (2019). A CRISPR–dCas Toolbox for Genetic Engineering and Synthetic Biology (Review) Journal of Molecular Biology 431(1): 34-47, 4 January, https://doi.org/10.1016/j.jmb.2018.06.037.

17 Vidyasagar, A. (2018). What Is CRISPR? Live Science April 20, https://www.livescience.com/58790-crispr-explained.html.

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TABLE 2
CRISPR/Cas9 key patent dispute timeline

May 2012
Charpentier and Doudna submit a patent application to the USPTO.

June 2012
The article by Charpentier and Doudna is published in Science: "A programmable dual-RNA guided DNA endonuclease in adaptive bacterial immunity."

December 2012
Zhang and colleagues submits a patent application to the USPTO.

January 2013
Zhang's article "Multiplex genome engineering using CRISPR / Cas systems" is published in Science.

April 2014
Zhang is awarded a patent by the USPTO.

April 2015
Charpentier and Doudna appeal the patent awarded to Zhang.

March 2016
Negotiations begin on who is the rightful holder of the CRISPR/Cas9 patent. Patent judges requested evidence from all parties.

February 2018
The European Patent Office (EPO) revokes the first of several CRISPR patents filed by Zhang and colleagues from the Broad Institute citing a clear lack of novelty.

March 2018
The EPO grants CRISPR co-inventor Emmanuelle Charpentier, together with the University of California and the University of Vienna, a broad patent covering the use of the CRISPR/Cas9 system for a new application beyond gene editing.

5. CLINICAL TRIALS UTILIZING GENE EDITING IN ADULT HUMANS

After the initial discoveries by Charpentier and Doudna, laboratories around the world stared to use CRISPR/Cas9 to change genes from in living organisms ranging from bacteria to monkeys. Recently, researchers in the US and China have started the first tests on humans. In principle, the CRISPR/CAs9 technology will make it possible to change human genes in a way that affects future generations.

The speed by which the CRISPR/Cas9 technology entered into clinical trials has been impressive. It is currently estimated that some 2,700 clinical trials using gene therapies are already under way or approved by regulatory authorities around the world.[23] Academia and pharma industry aim to combat diseases as diverse as cancer, muscular dystrophy and sickle cell anaemia.

Some of the indications where clinical trials are planned or on-going are outlined in Table 3.

Figure 3 Brian Madeux, a 44-year-old from Phoenix, Arizona, is suffering from the rare, life-threatening genetic condition Hunter's Syndrome since birth. In Nov 13, 2017 he became the first person in the world to undergo CRISPR/ Cas9 treatment that edited the disease related genes inside his body. Image from Annie Keller, Genetic Literacy Project, January 22, 2018

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TABLE 3
CRISPR/ Cas9 – Clinical applications and use

- **Disease where CRISPR/Cas9 technology has already been used**
- Hunter syndrome (metabolic disease)

- **Diseases in which which CRISPR/Cas9 gene editing could provide a cure**
- Cancer (selected forms)
- Cystic Fibrosis
- Haemophilia (type A and B)
- Beta-Thalassemia (blood disorder)
- Sickle cell disease
- Leber Congenital Amaurosis (Hereditary form of blindness)
- AIDS
- Muscle Dystrophy (Duchenne's)
- Huntington ´s Chorea
- Alpha-1 antitrypsin deficiency
- Amyloidosis (amyloid transthyretin)
- Mucopolysaccharidosis (types I and II)
- Primary hyperoxaluria type 1
- Severe combined immunodeficiency (SCID)
- Usher syndrome type 2a

The CRISPR technology has emerged from a natural defence mechanism, which allows many bacteria fight off viruses. This mechanism built on a function by which the bacteria were inserting fragments of viral DNA into specialized structures in their own genome (the "clustered regularly interspaced short palindromic repeats" that give CRISPR its name). By using this unique system, bacteria would provide their daughter cells with a way to recognize and halt future viral invasions. Once this long-overlooked mechanism was discovered, researchers realised that genome editing could be carried out in any species, including humans, simply by ting and editing sequences of DNA.

It was also early realised that the research findings could be turned into innovations and numerous potential clinical applications. After the first patient case in 2017, additional patients were enrolled in clinical studies in the US, which were carried out eight patients with Hunter syndrome and three with Hurler syndrome. Preliminary results showed that a few of the Hunter patients experienced a boost in the level of a missing enzyme, although levels did reach the normal level seen in healthy individuals. The preliminary results from the patients with Hurler syndrome showed clinical improvements.

6. MUCH AT STAKE AND A NEW JOB-MARKET EMERGING

Most of the small gene therapy companies behind the various CRISPR/Cas9 clinical trials have partnerships with Big Pharma, including companies such as Bayer, GlaxoSmithKline, Pfizer, Merck and Novartis. Within the Pharma and Biotech sector, several actors remain positive as regards future job opportunities. Several Big Pharma companies are today actively seeking to hire their own in-house gene therapy scientists.[24]

In addition to the Pharma sector, the demand for skilled genetic engineers in hospitals and laboratories is expected to soar, as more and more treatments relying on gene editing, move from research laboratories into hospitals around the world. Expectations are that there will also be a growing demand for clinicians as well as laboratory genetic engineers, who can interpret genetic information, offer support and advice to medical staff and guide patients. In the UK, the government predicts that by 2030, there may be more than 18,000 new jobs related to gene and cell therapy. In the US, the US Bureau of Labor Statistics estimates that during the next decade, around 17,500 new jobs will be created, with a 7% increase in jobs in the biomedical engineering sector and a 13% increase in the medical practice and sciences sector. In fact the US Bureau of Labor Statistics currently ranks genetic counsellors as one of the top 20 fastest growing jobs.[25]

7. A NOVEL TRANSFORMATIVE TECHNOLOGY FOR MEDICINE AND BIOTECHNOLOGY?

In addition to its medical use, the CRISPR technology has also successfully been applied in food and agricultural sciences and innovation projects.[26] For example, it has been applied to improve probiotic cultures and to engineer and vaccinate microbial functional food cultures (e.g. yogurt) against viruses. The CRISPR technology is also increasingly being used in modification of various crops in order to improve yields, enhance nutritional qualities and to improve tolerance to e.g. drought.[27]

Other potential applications include the creation of gene drives, which are genetic systems, capable of increasing chances of a particular genetic trait to pass on from parent to offspring. If successful, this could influence specific genetic traits to more easily spread within populations over generations. Such gene drives could influence or control the global spread of specific diseases such as malaria. The CRISPR technology could e.g. be used to enhance spread of sterility among the female Anopheles mosquito disease vector.[28] Alternative applications of CRISPR gene drives could be to introduce novel mechanisms in order to eradicate invasive vector borne disease or reverse pesticide and herbicide resistance.[29]

However, there are a number of drawbacks associated with the technology as well as its extended applications. One obvious limitation is that the CRISPR is neither specific[30] nor a 100 % efficient technology[31] and that the genome-editing efficiencies can vary. For example, in an early study conducted by Doudna and Charpentier, in rice, there were signs of gene editing in only approximately 50% of the cells that received the Cas9-RNA complex. Current evidence also indicate, that depending on the target, editing efficiencies may optimally amount to about 80%. In addition to the data showing a limited efficiency of the CRISPR/Cas9 technology, there is also a concern related to "off-target effects," where the host DNA is cut at sites other than the intended precise target. Such unwanted effects may potentially lead to the introduction of new and unintended mutations.[32] This effect may risk introduction of potentially random and dangerous genetic errors, an effect termed "genome vandalism".[33]

8. THE FIRST HUMAN EMBRYO GENE EDITING CONTROVERSY

In November 2018, before the Second International Summit on Human Genome Editing in Hong Kong, Chinese scientists became the first to report editing the genomes of human embryos. The research group was led by professor He Jiankui from the Southern University of Science and Technology in Shenzhen, PR China. The group under professor He claimed to have used the CRISPR gene editing technology to alter the DNA of human embryos during in-vitro fertilization. The project had resulted in the birth of twin girls. The objective was to remove a gene called CCR5, so the embryos might be resistant to potential infection with HIV/AIDS, since their father was HIV positive.[34]

The news sparked an immediate global debate about the ethical implications of such work. While some argued that gene editing in embryos could have a bright future since such technologies could eradicate serious genetic diseases prenatally, others argued that such work crossed an ethical line. There were earlier concerns that the genetic changes introduced to embryos, known as germline modification, could be heritable and thus cause an unpredictable effect on future generations.[35] In fact earlier researchers including the team of professor Huang had found a surprising number of 'off-target' mutations, which were assumed related to CRISPR/Cas9 acting on other parts of the genome in a complex way. This was put forward as a major safety concern related to human germline gene editing, since some of these unintended mutations could be harmful. A number of critical researchers and clinicians had previously argued that there was a need to pause further clinical research in order to solve a number of worries and outstanding issues.[36]

Figure 3 He Jiankui, announcing the first human CRISPR gene editing live births. Dr He carried out in-vitro fertilization gene editing to alter the DNA of human embryos. The objective, He said, was to remove a gene called CCR5, and the pregnancy resulted in the birth of twin girls. Public domain.

The human embryo editing by professor He aimed to use CRISPR to remove a single gene, so that the twin girls would be born immune to HIV after the CCR5 gene was altered in their genomes. However, the editing efforts did not appear to be fully successful, and in respect to the clinical indication, critical researchers argued that there were alternative and easier ways to prevent HIV infection. Many of the critics also argued that the twins were the un-consenting subjects of a researcher who had the ambition to be a "scientific first," hoping for international scientific recognition.

9. IS THERE A NEED TO SET LIMITATIONS FROM AN ETHICS AND MORAL PERSPECTIVE?

The expanding number of potential applications of the CRISPR technology have increasingly raised questions about the ethical and moral consequences of altering the genome of humans and other living organisms. The variable efficacy, potential off-target effects and imprecise gene edits all represent potential safety concerns.

For example, there are potential yet unknown ecological impacts of the use of gene drives.[37] A trait introduced, either by intention or emerging un-intentionally from the use of the CRISPR technology, could spread beyond the target population and into other organisms through cross-breeding. Alternatively, over generations, the use of gene drives could reduce the genetic diversity of target populations. Particular care has to be considered when the intention is to make genetic modifications in human embryos and reproductive cells such as sperm and eggs, known as germline editing. Since such germline changes can be passed on to coming generations, an extended and liberal use of CRISPR technology in humans is currently raising an increasing number of ethical concerns in the scientific community.38

In addition to the concerns yet raised, there is much related to the CRISPR technology that is still unknown to science. Therefore, groups of scientists, ethics and legal experts[39] argue that germline editing raises concerns of unintended consequences for future generations since there are fundamental limits in the knowledge of human genetics, gene-environment interactions, and the pathways of disease (including the interplay between one disease and other conditions or diseases in the same patient). Such ethical concerns need to be discussed, since we risk introducing genetic traits that could fundamentally affect the future generations without having their consent. Also, the possibility that germline editing could be used as an enhancement tool for various human characteristics may also raise concerns.[40]

To identify potential and emerging areas of conflict and concerns, governmental and institutional bodies such as US National Academies of Sciences, Engineering and Medicine have issued a comprehensive report with guidelines and recommendations for genome editing. Although several actors urge caution in exploring germline editing, it does not mean prohibition. One recommendation has been that germline editing should first be done on genes leading to serious diseases and only when there are no other known or reasonable treatment alternatives. Also, there will also be a need to closely and carefully monitor potential health risks and benefits associated with trials in humans or any other living organism. This also include following up on families for multiple generations and environmental impact long-term.

10. PRESENT AND EMERGING PATENT LANDSCAPE AND POTENTIAL FUTURE COMMERCIAL APPLICABILITY

Research and innovation related to CRISPR has tended to speed up during recent years. Although the initial patents remain important pieces of intellectual property related to the CRISPR technology, their full importance and commercial value remains to be seen. The patent landscape is today becoming increasingly complex, with multiple companies, major universities and research institutes, as well as research groups and individuals claiming key parts of CRISPR/Cas9 patent protection. (Figure 4).

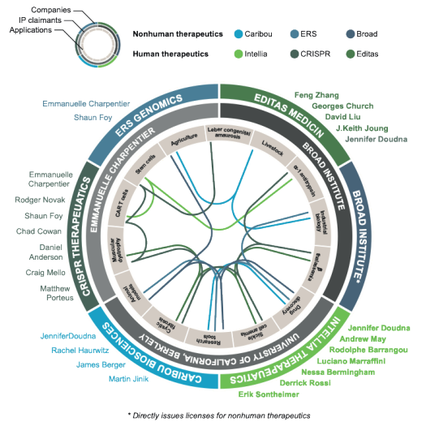

Figure 4. A graphic overview of current CRISPR/Cas9 patenting
From reference 41; Rodríguez Fernández C. Doudna and Charpentier Get Second CRISPR Patent in Europe.
From https://labiotech.eu/policy-legal-finance/doudna-charpentier-crispr-patent-europe/ March 01, 2018

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32 Shwartz, M. (2018). Target, delete, repair. CRISPR is a revolutionary gene-editing tool, but it's not without risk, Stanford Medicine Winter 2018. https://stanmed.stanford.edu/2018winter/CRISPR-for-gene-editing-is-revolutionary-but-it-comes-with-risks.html.

33 Kosicki, M., Tomberg, K. & Bradley, A. (2018). Repair of double-strand breaks induced by CRISPR–Cas9 leads to large deletions and complex rearrangements. Nature Biotechnology 2018: 36; 765–771 https://doi.org/10.1038/nbt.4192, Grant, B. (2015). Credit for CRISPR: A Conversation with George Church. The Scientist Dec 29, 2015. https://www.the-scientist.com/news-analysis/credit-for-crispr-a-conversation-with-george-church-34306 and Le Page, M. (2018). CRISPR gene editing is not quite as precise and as safe as thought. New Scientist 16 July 2018. https://www.newscientist.com/article/2174149-crispr-gene-editing-is-not-quite-as-precise-and-as-safe-as-thought/.

34 Cyranoski, D. (2018). CRISPR-baby scientist fails to satisfy critics. Nature November 28, https://www.nature.com/articles/d41586-018-07573-w.

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40 Ibid.

41 The National Academies of Sciences, Engineering and Medicine (2017). Committee on Human Gene Editing: Scientific, Medical, and Ethical Considerations. http://www8.nationalacademies.org/onpinews/newsitem.aspx?RecordID=24623.

Adding further to the complexity of the CRISPR technology platform, the EPO has in 2017 granted a broad patent covering the use of the CRISPR/Cas9 system for new applications beyond gene editing to Emmanuelle Charpentier together with the University of California and the University of Vienna as co-inventors. This new CRISPR patent covers the use of a chimeric Cas9 enzyme, modified to inactivate its DNA-cutting function. Further, in January 2018, the EPO also revoked the first of several CRISPR patents filed by the Broad Institute citing a clear lack of novelty. This decision was a big win for Charpentier and Doudna, in the fight for the ownership of the patent rights against Feng Zhang and the Broad Institute related to ownership of technology behind CRISPR.

In addition, the EPO granted CRISPR co-inventor Emmanuelle Charpentier, together with the University of California and the University of Vienna, a broad patent in 2018 covering the use of the CRISPR/Cas9 system for a new application beyond gene editing. Of importance for claiming priority is that Cas9 enzyme can be combined with a protein domain that either activates or inhibits the expression of the gene targeted by CRISPR without modifying its sequence. This technology is known as CRISPR-a (activating CRISPR) and CRISPR-i (inhibitory CRISPR).[42] The new patent approved EPO will cover gene regulation using CRISPR/Cas9 in multiple settings, such as in bacteria, plants, animals, as well as human cells. This specific CRISPR patent covers the use of what is called chimeric Cas9 enzyme, which is modified to inactivate its DNA-cutting function. The most important application of this form of CRISPR/Cas9 is in gene regulation. Thus, Zhang seems to be on the winning side so far in the US, but the decisions of the EPO are so far benefitting the Doudna-Charpentier team.

11. PATENTING RELATED TO CRISPR TECHNOLOGIES WILL REMAIN A DYNAMIC AREA FOR MANY YEARS TO COME

It is becoming increasingly clear that there will be major and important life sciences applications emerging from the CRISPR/Cas9 and related technologies in gene regulation. In addition to its wide application in research, emerging CRISPR technologies are likely to be increasingly used in drug discovery and therapeutics as well as in plant and animal breeding.[43] Novel tools based on these findings are becoming widely used in research, particularly for drug discovery. Using libraries of CRISPR targets, such tools may be used to find genes that e.g. enhance the effect of available cancer drugs when specific genes are activated or inactivated. While there are possible therapeutic applications of this form of CRISPR, the biggest potential seems to be in research for now.

The different positions taken by the US and European patent offices are clearly polarizing the CRISPR field. If such trends continue, it may imply, that depending on where you use CRISPR in the world, there will be a need to obtain licenses from the other party. This is likely to increase transaction costs and make it more difficult and expensive for commercial actors to initiate international product development programs within the CRISPR/Cas9 area.[44]

12. CONCLUSIONS AND VISIONS

The discovery of the CRISPR/Cas9 system and realisation of its fundamental biological role and mode of action is likely to change medicine and biotechnology in many respects.

In this review, we have described some of the recent discoveries from the fundamental basics of the system as well as some of the potential uses of CRISPR/Cas9 and related systems, as tools to perform genome editing in medicine and various fields of biotechnology and medicine. In particular, we have addressed the patent aspects related to its discovery and some aspects of the recent legal disputes.

The various CRISPR technologies evolving from the initial CRISPR/Cas9 discovery provide opportunities for developing a "search and replace function" for a variety of DNA strands. Simply put, the technologies evolving from this research may allow for replacement of disabled or dysfunctional genes by new DNA letters in order to change or normalize biological function. At the present early stage of development of the various technology applications, we do not exactly know what novel treatments or benefits this technology will offer clinical medicine in the end.

In an optimistic scenario, the technique may provide radical treatment options for a range of severe genetic diseases, where treatments are currently lacking or are suboptimal. Further, in e.g. transplantation medicine there are hopes that the CRISPR/Cas9 technology could enable us to genetically engineer pigs or other animals so that they can become suitable organ donors to humans. Within vector borne diseases, such as malaria, there is ongoing research to modify the vectors, so that they may not be able to transmit human diseases. In laboratory and diagnostic medicine, there are reasons to believe that CRISPR technologies may realize a number of potential applications and improved techniques.

Further, within plant breeding, there are research and innovation efforts to use the CRISPR technology to eradicate various pests by genetically modifying plants to withstand attacks.

An interesting area, currently under serious exploration, is the CRISPR technologies may provide a new tool for biodiversity conservation and de-extinction, i.e. the possibility to conserve endangered species and even bring back extinct animal species, such as the passenger pigeon and the woolly mammoth. Although this may sound like science fiction, there are hopes (and fears) that the resurrection of extinct species may soon be reality.

However, within all medical or biological areas of application, there are a number of ethical problems that needs to be addressed and clarified. While the CRISPR/Cas9 discoveries are offering a number of potential game-changing opportunities within Life Sciences, the perceived risks and potential rewards may vary greatly between applications. Also estimated and perceived long-term values may vary significantly between stake-holders, such as the individuals, regulators, companies involved as well as society at large. Since numerous potential applications of the CRISPR/Cas9 technology are already underway, we may expect an increased public awareness and debate related to the CRISPR/Cas9 technology area within the near future.

Today, the patent landscape related to CRISPR/Cas9 technology is becoming increasingly complex. For any party successful in claiming IP, there may be opportunities to claim rights to an innovation platform that may turn out be one of the most important genetic engineering techniques in recent biotechnology. Thus, anyone who can claim key patents in one or several areas, may look forward to significant rewards if or when such applications start to become commercial. In 2018 we saw major legal conflicts evolving from disputes between the some of the early actors and their host institutions claiming patent rights. Since major work and funding are focussed on patenting the key technologies and applications related to the biological CRISPR/Cas9 platforms, there are reasons to believe that there may be additional disputes coming in order to gain a monopoly position which may allow for future benefits and profits from the technology. However the road to future profits from the CRISPR in any technology field or area is difficult and expensive. Extensive funding and major commitment to development will be required to reach the various commercial applications.

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Being equitable about equivalents

By John Hornby

1. UNINTENDED CONSEQUENCES?

Has Lord Neuberger in *Actavis*[1] introduced "an amorphous general inventive idea"[2] test to determine UK patent infringement by equivalents? Are "inessential integers", once found extremely rarely[3], now to be embraced as part of normal UK practice? Have UK patent claims become "a puzzle game"?[4]

Lord Neuberger, clearly did not believe that he had changed UK law considerably with his decision in *Actavis* or that the decision would have a substantial impact. At a UCL conference[5] following *Actavis*, he referred to *Kirin-Amgen*[6] (the previous leading authority on infringement in which purposive construction was confirmed as the correct approach) as having been *"slightly wrongly"* decided. He also remarked upon *"the relative infrequency with which equivalents are applied in other jurisdictions where they have been accepted."* However, having adopted an equivalency test, the point is coming up frequently in UK cases and those cases appear to be suggesting that the answers to some of the above questions are "yes". Generalised ideas, inessential integers and puzzles have all become part of the landscape.

2. THE ACTAVIS QUESTIONS AND WHY THE FIRST IS KEY

There are three equivalency test questions but it is the first that, in the cases decided post-*Actavis*, has been key. Why?

The questions are:

> *"i) Notwithstanding that it is not within the literal meaning of the relevant claim(s) of the patent, does the variant achieve substantially the same result in substantially the same way as the invention, ie the inventive concept revealed by the patent?*
>
> *ii) Would it be obvious to the person skilled in the art, reading the patent at the priority date, but knowing that the variant achieves substantially the same result as the invention, that it does so in substantially the same way as the invention?*
>
> *iii) Would such a reader of the patent have concluded that the patentee nonetheless intended that strict compliance with the literal meaning of the relevant claim(s) of the patent was an essential requirement of the invention?"*[7]

Before turning to the individual questions, a marker is appropriate regarding the meaning of "variant". Lord Neuberger used the *Improver*[8] questions (directed at determining purposive construction) as his starting point for setting out the UK equivalency test. In those questions, Hoffmann, J. (as he then was) defined the word "variant" as follows:

> *"a feature embodied in an alleged infringement which fell outside the primary, literal or a contextual meaning of a descriptive word or phrase in the claim ('a variant')."*

However, in *Actavis*, Lord Neuberger's "variant" must be referring to more – at least to all the features of, or corresponding to, those of the inventive concept. The relevance of other features is addressed below when dealing with Question i). In what follows, "variant feature" is used to describe a variant as the term was used in *Improver*.

Question ii) assumes that: the variant achieves substantially the same result in substantially the same way as the inventive concept revealed by the patent; and the person skilled in the art would know that it achieves that result. The question asks if it would have been clear to the person skilled in the art at the priority date that the alleged infringement achieves that (i.e., substantially the same result) in substantially the same way as the inventive concept revealed by the patent.

How might a negative answer be achieved to Question ii)? In Actavis (at paragraph 64), Lord Neuberger, considered whether a variant that was itself inventive would lead to such an answer, reflecting what he found was sometimes the case in Germany. However, whilst not deciding the point, he said that he was not sure that requiring the variant to be non-inventive was "appropriate".[9]

Of Question ii), Arnold, J. observed recently:

> *"There are likely to be few cases in which this question will be answered in the negative."*[10]

Notwithstanding that each case turns on its own facts, the skilled person's lack of understanding of how the variant works on the assumptions to be made, whilst logically possible, would seem to be improbable. The Judge went on to hold *"In the present case the answer must be yes."* And, so it must be (in the author's view) in the vast majority of cases.

Question iii) again derives from the Improver questions. However, rather than asking whether strict compliance with claim language was intended by the patentee (perhaps more accurately the patent applicant)[11], the question asks whether the patentee intended that such strict compliance was an essential part of the inventive concept. The difficulty with the question is that, for it to be answered in the affirmative, one has to be prepared to revisit the question of what the inventive concept is. If not, the answer to the question has to be "no" and the question is redundant.

Looked at one way, question iii) is asked as a check that the Court has correctly identified *"the inventive concept revealed by the patent"*, as required by question i). In the post-*Actavis* cases, Question iii) has received little attention and the author suggests that this is because the Courts have not been prepared to go back and consider what the patentee was putting forward as the relevant invention.[12] And that brings us to how the UK Courts have, post-*Actavis*, gone about identifying inventive concepts under Question i), including the weight attached to what the patentee states about the matter in the patent.

3. QUESTION I) AND DETERMINATION OF THE INVENTIVE CONCEPT IN ACTAVIS

That the *Actavis* questions will need some "interpolation" has already been stated by the Court of Appeal. So, the reference to "literal meaning" in question i) has been said to mean "normal meaning"[13]. The same point may later be made about question iii), should the Courts ever look closely at that question.

Also, there is then the question as to whether "normal meaning" is exactly the same as the old purposive construction explained in *Kirin-Amgen*. That the word "normal" implies a purposive approach has been said by the Courts on several occasions[14] but it has also been doubted that it is the same purposive construction as under the old law.[15]

There are, however, some more significant questions.

(1) How is an inventive concept to be identified?
(2) Of what significance are integers of the claim that are not part of the inventive concept?

Regarding (2), if certain integers are excluded altogether from an inventive concept, then features (if any) of the alleged infringement corresponding to those integers are highly unlikely to be of any relevance. Once excluded, they won't impact significantly (or more likely, at all) on the result of using the relevant inventive concept or the way in which that result is achieved. Those features, and their effects, can then easily be disregarded, as will become clearer later when specific post-Actavis cases are considered.

This highlights the paramount importance of question (1). An unduly broad inventive concept will lead to a correspondingly broad "effective claim" for the purposes of the doctrine of equivalents, without further curtailment by the language of the actual claim.[16] In sum, those integers not within the inventive concept, and corresponding features (if any) of the alleged infringement, can readily be ignored altogether – i.e., rendering the claimed integers truly inessential.

Turning to question (1) above (how to identify an inventive concept), Lord Neuberger does not set out detailed guidance as to what he meant by "inventive concept" (or his alternative phrase, "inventive core"). He did refer to authorities from other European Patent Convention (EPC) states in formulating the UK equivalency test but he recognised that there was no uniformity of approach in those states (paragraph 32). He didn't cite any definition of "inventive concept" from Dutch law, where that phrase is used (paragraph 51), or of "inventive core" from Italian law, where that phrase is used (paragraph 48).

1 Actavis v Eli Lilly [2017] UKSC 48.
2 The Swedish Doctrine of Equivalence (2011) by Professor Bengt Domeij, Uppsala University, top of page 3, available in English at http://uu.diva-portal.org/smash/get/diva2:391087/FULLTEXT01.pdf.
3 Patents for Inventions, Blanco White, 5th Edition, paragraph 2-111.
4 Napp v Dr Reddy's [2016] EWCA Civ 1053 at paragraph 71 per Floyd L.J. "A patent specification is not intended to be a puzzle game in which the skilled person must come up with his own theory as to what degree of precision was intended by the patentee."
5 University College London conference, 1 Nov 2017, "Equivalents: K = Na. Is the Genie out of the Bottle?". Available on line - see at about 1hr, 6mins: www.youtube.com/watch?v=y84hUeArgMs&feature=youtu.be
6 Kirin-Amgen v Hoechst Marion Roussel [2005] RPC 9.
7 Paragraph 66 of Actavis.
8 Improver v Remington [1990] FSR 181 at 189.
9 Note that, as a practical matter, it may be difficult for the alleged infringer to maintain that its variant is inventive, whilst the patentee's alleged invention was not. In other words, the alleged infringer may be forced to elect early on whether to say that both its variant and the claimed invention are obvious or both are inventive.
10 Eli Lilly v Genentech [2019] EWHC 387 (Pat) at paragraph 598, discussed further below.
11 However, patentee is used in this article since that is the word used in the Judgments cited and quoted.
12 See, for example, paragraph 70 of Icescape v Ice-World [2018] EWCA Civ 2219 discussed below.
13 Paragraph 66 of Icescape (ibid).
14 Mylan v Yeda [2017] EWHC 2629 at paragraph 138, Illumina v Premaitha [2017] EWHC 2930 at paragraph 201, Icescape at paragraph 60.
15 Eli Lilly v Genentech [2019] EWHC 387 (Pat) at paragraph 294: "As HHJ Hacon sitting as a High Court Judge pointed out in Regen Lab SA v Estar Medical Ltd [2019] EWHC 63 (Pat) at [202]-[207], it is no longer necessary to take equivalents into account in such an interpretation, because it is now possible for a patentee to contend that a patent has been infringed by virtue of the doctrine of equivalents even if it is not infringed when the claims are given a normal interpretation." See too HHJ Hacon in Coloplast v McGregor Healthcare [2018] EWHC 2797 at paragraph 71.
16 Subject to questions ii) and iii), whose significance is limited, as discussed earlier.

In *Actavis* itself, claim 1 of the patent[17] was in Swiss form and called for a combination of pemetrexed disodium and vitamin B12 (or a derivative). Equivalency concerned the substitution of a sodium ion with other counter-ions (potassium being one). Lord Neuberger held:

> *"... the inventive concept of the patent is the manufacture of a medicament which enables the pemetrexed anion to be administered with Vitamin B12 ...". (Paragraph 61.)*

Although Lord Neuberger did not explain how he reached that conclusion, finding the sodium ion not to be part of the inventive concept was entirely consistent with the patent's teachings (e.g., at paragraph 16). It is clear that the pemetrexed anion, formed on disassociation of the sodium salt in solution, was key but that the identity of the specific counter-ion (sodium) was not. Lord Neuberger also referred to common general knowledge (CGK), such as the trial Judge's findings about potassium salts (paragraph 26(ii)):

> *"... generally soluble, but there were exceptions. There were concerns about the potential toxicity of such salts, which was particularly significant if large quantities of the drug were involved."*

However, it is not clear if, or how, findings of the trial Judge about CGK influenced the identification of what constituted the inventive concept, as opposed to Lord Neuberger's general understanding of the specification. Certainly, there is no indication that he used it for the purposes of ignoring altogether the reference to sodium. And one could point to the ions of potassium, tromethamine or (in the case of the free acid infringement) hydrogen as being corresponding features to the sodium ion. Nonetheless, it does leave open the question of whether other counter-ions could have been substitutes. However, as a practical matter, only those counter-ions that didn't significantly affect the action of the pemetrexed ion would be likely to ever come before a Court.

4. GUIDANCE ELSEWHERE

The phrase "inventive concept" is used, both in the Patents Act, 1977 and in case law, to assist in the determination of other issues concerning UK patents. Lord Neuberger, having presided in the Patents Court on many occasions, would have been sufficiently familiar with UK patent law to know that.

4.1 Unity of invention

Sections 14(5)(d), (6), 17(6) and 26(b), which concern unity of invention, are the only sections in the Patents Act, 1977 that refer to the phrase "inventive concept". S.14(5) provides:

> *"The claim or claims shall ... (d) relate to one invention or to a group of inventions which are so linked as to form a single inventive concept." (Also see Art. 82 EPC.)*

Rule 16 of The Patents Rules, 2007 (see too EPC, Rule 44) provides some guidance as to how this should be done, and this is reflected in the UK Manual of Patent Practice (14.158):[18]

> *"One criterion which would be suitable for some sets of claims would be to determine whether the common subject-matter of the claims is novel and involves an inventive step."*

So, here "inventive concept" is to be determined by reference to patentability in the light of the state of the art. However, and as discussed below, that does not appear to how the phrase is (or ought to be) used in other areas of UK patent law. Unity has its own statutory definition and, in the author's view, should be ignored for the purposes of considering how the phrase "inventive concept" should be construed when applying the doctrine of equivalents.

4.2 Inventive step

Lord-Justice Jacob re-formulated the *Windsurfing*[19] approach, often used[20] in the UK to assess obviousness, in *Pozzoli SPA v BDMO SA [2007] EWCA Civ 588* at paragraph 23:

> *"(1)(a) Identify the notional 'person skilled in the art';*
>
> *(b) Identify the relevant common general knowledge of that person;*
>
> *(2) Identify the inventive concept of the claim in question or if that cannot readily be done, construe it;*
>
> *(3) Identify what, if any, differences exist between the matter cited as forming part of the "state of the art" and the inventive concept of the claim or the claim as construed;*
>
> *(4) Viewed without any knowledge of the alleged invention as claimed, do those differences constitute steps which would have been obvious to the person skilled in the art or do they require any degree of invention?"*

Given that identifying the inventive concept is done at a stage prior to determining inventive step, it would seem tolerably clear that the terms do not mean the same thing, at least in this context. However, one can find judicial pronouncements suggesting otherwise, notably in *Generics (UK) v Lundbeck [2009] UKHL 12*, a case concerning insufficiency mentioned further below and in which Lord Neuberger was one of the members of the Appellate Committee.[21]

In Pozzoli, Jacob, L.J. gave some guidance as to how to identify the inventive concept, which included (underling added):

- *"... it is only through the eyes of the skilled man that one properly understand what such a man would understand the patentee to have meant and thereby set about identifying the concept." (Paragraph 15.)*
- *"So what one is seeking to do is to strip out unnecessary verbiage, to do what Mummery L.J. described as make a précis." (Paragraph 18.)*
- *"... if a disagreement about the inventive concept of a claim starts getting too involved, the sensible way to proceed is to forget it and simply to work on the features of the claim." (Paragraph 19.)*
- *"Identification of the concept is not the place where one takes into account the prior art. You are not at this point asking what was new. Of course the claim may identify that which was old (often by a pre-characterising clause) and what the patentee thinks is new (if there is characterising clause) but that does not matter at this point." (Paragraph 21.)*
- *"In the end, to my mind, what the skilled man's take-home message from the claim in the context of the patent is, is really no more than "overlap the discs, hold them in the known way via their centres yet space them via a step-like arrangement so they can be got out." (Paragraph 49, underlining added.)*

So, although one can find statements that indicate differently, here the focus appears to be on what the patentee has put forward as his invention,[22] rather than identifying differences between the claims and the state of the art. Note too that the exercise might only entail removing verbiage from a claim and that one might just revert to the claim as a whole.

4.3 Entitlement

In entitlement disputes, the Courts seek to identify contribution(s) to the "inventive concept" by the relevant parties. Here, perhaps more than elsewhere, the cases are not consistent as to what the phrase means and what follows only comprises some highlights. Importantly, these disputes may be decided before grant and before there are any claims. In the latter case, there is little option but to look at what the patentee says in the patent's description for guidance as to the identity of the inventive concept.

The House of Lords case of *Yeda v Rhone-Poulenc [2007] UKHL 43* provides guidance on the meaning of the phrase "inventive concept" as it is used in the context of entitlement. Lord Hoffmann held at paragraph 20:

> *"It is not enough that someone contributed to the claims, because they may include non-patentable integers derived from prior art."*

[17] European Patent (UK) No 1,313,508.[18] See too W 0006/97 (Foamed pressure sensitive tapes) of 18.9.1997, paragraph 6.4.

[19] Windsurfing International v Tabur Marine [1985] RPC 59.

[20] For the most recent guidance as to how UK Courts should assess inventive step, see the Supreme Court Judgment in Actavis v ICOS [2019] UKSC 15 at paragraph 60 onwards.

[21] Lord Neuberger equates the terms inventive concept and inventive step at paragraph 101 and Lord Walker says that inventive concept is that "which entitles the inventor's achievement to be called inventive" (underlining added) at paragraph 30. Contrast too Lord Walker's description of the inventive concept at paragraph 28 with the trial Judge at paragraph 75(i), [2007] EWHC 1040 (Pat).

[22] See also Laddie, J.'s statement in Brugger v Medic-Aid [1996] RPC 635 at 656 (decided before Pozzoli):
"The important issue as far as this case is concerned is to identify correctly the inventive concept which the patentee must be taken to have put forward as underpinning his monopoly."

However, not only is the statement difficult to understand, but also strictly speaking it was probably made obiter (since the Court's decision did not appear to call for determination of the precise point). Further, in *Welland Medical Limited v Philip Arthur Hadley [2011] EWHC 1994 (Pat)*, Floyd, J. referred to paragraph 20 of Yeda and held (at paragraph 21):

> *"I do not think that in this passage Lord Hoffmann was saying that one determines entitlement to subject matter in a patent application by reference to any detailed analysis of validity in relation to the prior art."*

Prior to that decision, in *Markem Corporation v Zipher Limited [2005] R.P.C. 31*, Jacob, L.J. (giving the Judgment of the Court of Appeal), at paragraph 103 endorsed the following statement made in an earlier first instance decision:[23]

> *"... it is the inventive concept or concepts as put forward in the patent with which one is concerned, not their inventiveness in relation of the state of the art."*

The Deputy Judge in that earlier case repeated the same point elsewhere in his Judgment.[24]

However, one year after Markem, in IDA Ltd v The University of Southampton [2006] EWCA Civ 145, Jacob, L.J., giving the Judgment of the Court of Appeal, held:

- *"All that Professor Howse added to Mr Metcalfe's idea is the common general knowledge of those in the art. There was nothing inventive about it and I do not see how Professor Howse could fairly be described as an inventor. The "heart" was Mr Metcalfe's idea and his alone." (Paragraph 33.)*

- *"Normally the addition of matter which is common general knowledge is the sort of thing often forming the subject of subsidiary claims of no significance as regards inventorship. Persons skilled in the art naturally add common general knowledge to their key ideas. The fact that here such an addition goes to the generality of the main concept and claim should not, and in my view does not make any difference." (Paragraph 37.)*

It is hard to reconcile the statements of Jacob, L.J. in *IDA* with what he said in *Markem*. (Note here that, of course, the state of the art referred to in *Markem* includes the CGK referred to in *IDA*.) Further, at paragraph 43 of *IDA*, Jacob, L.J. appears to go further and equate the way in which "inventive concept" is used in entitlement to that used to determine unity. In the author's view, the latter cannot be right and the approach endorsed in *Markem* is to be preferred to that in *IDA*. As Pumfrey, J. held in *Collag v Merck [2003] F.S.R. 16* (paragraph 79):

> *"... I should point out where there are a number of different contributions to the inventive concept described in a patent application, I do not think that it is correct to look only at the contributions that are inventive."*

It follows that the inventive concept could, for example, include aspects of the relevant CGK.

4.4 Repair

Earlier in this article, reference is made to Lord Neuberger's familiarity with the phrase "inventive concept" in other areas of UK patent law. In *Schutz (UK) Ltd v Werit (UK) Ltd [2013] UKSC 16*, he gave the lead Judgment of the Supreme Court in a case concerning alleged infringement by repairing a patented article. At paragraph 67, he held:

> *"... that it must be legitimate, in the context of addressing the question whether a person "makes" the patented article by replacing a worn out part, to consider whether that part includes the inventive concept, or has a function which is closely connected with that concept."*

Then, at paragraph 69, he went onto explain:

> *"In almost all patents, the claimed inventive concept is clearly identified or identifiable from the patent, and, if it is unclear or disputed, it will often be an issue in the proceedings anyway."*

The above statement appears to be entirely consistent with the approach of Jacob, L.J. in *Pozzoli*, referred to earlier in the context of inventive step. It is also consistent with the same Judge's statement in *Markem*, regarding entitlement. But, is it the approach that the Courts have adopted post-*Actavis* in the context of equivalents? In the author's view it makes sense to use the term in the same way for validity, ownership and infringement.

5. POST-ACTAVIS DECISIONS

5.1 Icescape v Ice-World International [2018] EWCA Civ 2219

The decision in *Icescape* was made by a strong Court of Appeal. The Court's approach to identifying an inventive concept for equivalency bears little resemblance to that in *Markem* or *Pozzoli*. However, the Court in *Icescape* does not explain the basis, by reference to authorities or otherwise, for adopting its approach.

The patent[25] in *Icescape* concerned an arrangement of pipes for providing coolant to an ice rink, designed to have foldable components and be easily transported, whilst retaining fluid tight connections in use. The patent explained (at paragraph 4) that the aims of the invention were to allow rapid installation, reliable operation, differing skating area coverage and substantial/complete coolant recovery.

Claim 1 had a pre-characterising portion and, as broken down by the trial Judge, five characterising features. The infringing arrangement did not have characterising features D and E, which the Court found (at paragraph 70) on a normal construction required cooling elements to be connected in series. As a result of its different configuration, the assembly incorporated elements connected in parallel. Also, it meant that (paragraph 53):

> *"... the whole assembly is more complicated as a result of the extra piping and will take longer to install and break down, contrary to the purpose of the patent." (Underlining added.)*

Indeed, whilst a parallel configuration leads to a more even distribution of cooling, the disadvantage referred to above is also an inevitable consequence.

The trial Judge found that all of the features of claim 1 were part of the CGK with the exception of characterising feature C, which concerned a folding joint.[26] Against that background, the Court of Appeal found that feature to be the inventive concept.[27] Having stripped out the CGK, the effects of the variant feature (of integers D and E) were dismissed, and infringement found, because that variant feature (in Lord Kitchin's words) *"has nothing to do with the inventive core of the patent"*. (However, the patent was found invalid for lack of novelty due to the failure of a crucial priority argument.)

And in paragraph 74, Lord Kitchin dealt with the third *Actavis* question, seemingly in a way that could only lead to a negative answer because the identification of the inventive concept was not substantively re-addressed:

> *"There is no reason why the skilled reader would have thought that strict compliance with integers D and E was an essential requirement of the invention. The inventive core of the patent has nothing to do with the coupling of the elements together or whether the fluid flows through them in series or in parallel."*

In sum, to identify the inventive concept, the Court: stripped out from the claim what had been found to be CGK (c.f., acknowledged as known in the patent); ignored that the relevant features were characterising features of the claim; and ignored that the features corresponding (at one level of generality) to those of the claim not within the inventive concept were more complicated and took longer to install and breakdown (i.e., more laborious and expensive), "contrary to the purpose of the patent".[28]

As suggested earlier, it makes sense to have the same meaning attributed to inventive concept for obviousness and equivalents. However, the *Icescape* approach to identifying an inventive concept (for equivalents) is in conflict with the *Pozzoli* inventive step test (paragraph 23, quoted above).

First, if CGK is to be stripped out from a claim, why not other state of the art? If that were done, the *Pozzoli* test would be rendered inoperable. Second, how is *Pozzoli* to be applied when the invention comprises combining features that are individually CGK?[29] Third, and related to "second", how should the Court approach *Pozzoli* when the obviousness attack is based on CGK alone?[30]

There is clearly an increased danger, if the *Icescape* approach is adopted, of salami slicing claims into bits of CGK and bypassing, not just what the inventor claims to be his invention, but also the inventor's inventive step (if any). Note here that, in the *Pozzoli* test, the skilled person uses his CGK to understand the patent, not in an exercise of stripping it out of a claim to identify its inventive concept. (See the quoted passages from *Pozzoli* earlier.)

Further, what of Article (2) of the Protocol to EPC, Article 69? It provides:

> *"For the purpose of determining the extent of protection conferred by a European patent, due account shall be taken of any element which is equivalent to an element specified in the claims."*

This clearly envisages identifying corresponding (equivalent) features in the alleged infringement to each of the integers of the relevant claim. It doesn't contemplate ignoring claim integers altogether, although admittedly the distinction may depend on the level of generality to which one descends.

[23] Stanelco's Application [2004] EWHC 2263 at paragraph 15.

[24] "The Court is not concerned with issues of validity or inventiveness: merely with the concept as described." (Paragraph 12.) "This enquiry does not involve any assessment of whether the invention represents a contribution to the art, or an inventive contribution (in the obviousness sense) to what the other inventor has come up with. ... What is relevant is what is put forward in the patent as inventive...". (Paragraph 18.)

[25] EP (UK) 1,462,755.

[26] Recorded in paragraph 16 of the Court of Appeal judgment.

[27] Lord Kitchin at paragraph 72 and Floyd, L.J. at paragraph 98.

[28] Nor was any substantial attempt made to identify equivalent features in the allegedly infringing device to those of the claim (but, as mentioned elsewhere in this article, such an exercise may depend on the level of generality with which one approaches it).

[29] See Accord Healthcare v Medac [2016] EWHC 24 (Pat) at paragraph 122: "Many inventions involve a combination of known features. However a combination of features, all of which individually were common general knowledge, can give rise to a valid patent claim if that combination is new and non-obvious."

[30] In Ratiopharm v Napp [2008] EWHC 3070 (Pat), Floyd, J. identified an inventive concept (paragraph 160) for the purposes of considering the Pozzoli test in an attack based on CGK alone. He then went onto consider the difference between that concept and the CGK (paragraphs 206 et seq), pursuant to the third Pozzoli step.

5.2 Regen Lab v Estar Medical [2019] EWHC 63 (Pat)

Regen's patent[31] claimed a method for the preparation of a blood plasma which was enriched in platelets and other blood factors, known as platelet rich plasma, or PRP. Claim 1 comprised steps of centrifuging blood, separating plasma from the erythrocytes and resuspending the enriched plasma. Specifically, it included the step of:

> *"a) Centrifuging whole blood in a separator tube selected from:*
> *- a glass separator tube containing a polyester-based thixotropic gel and a buffered sodium citrate solution at 0.10M ..." (underlining added).*

HHJ Hacon explained (paragraph 226):

> *"The Defendants' case on non-infringement was:*
>
> *(1) the thixotropic gel of their product was not polyester-based; and*
>
> *(2) the buffered sodium citrate solution was at 0.136M, not 0.1M as required in claim 1." (Note that, in fact, the claim called for 0.10M.)*

Regen's principal case on infringement was based on equivalents and HHJ Hacon emphasised his view of the need to identify clearly the inventive concept for that purpose at paragraph 234:

> *"Sometimes during argument in the present case the inventive concept was identified by restating practically the entirety of the claim. This did not focus matters. It is both helpful and necessary to simplify the inventive concept as much as can accurately be done."*

The author questions what basis there is for this judicial statement about the necessity to simplify the inventive concept. Further, in the author's view, this desire to simplify claims has developed into a determination to find reasons to root out integers of claims, which has led to overly broad inventive concepts being found with no foundation in the patent itself. Further, as pointed out earlier, once integers have been rooted out, their effects, and those of any corresponding features of the alleged infringement, can easily be ignored.

At paragraph 222, the Judge explained what he considered, in general terms, to be an inventive concept:

> *"I take the inventive concept or core of the invention to be the new technical insight conveyed by the invention – the clever bit – as would be perceived by the skilled person. This will be assessed by reference to the specification and the evidence."*

However, that explanation raises the questions: "clever in the light of what?"; and "evidence of what?" Again, this test does not appear to be in line with either *Pozzoli or Markem*, since it appears to be looking for something which is inventive over the state of the art.

The Judge went on to set out what he considered to be the inventive concept of claim 1 at paragraph 235:

> *"... the preparation of PRP for solely therapeutic use by employing a thixotropic gel wherein (a) there is only one centrifugation and (b) after centrifugation about half the supernatant is removed and the platelets are then re-suspended in the enriched plasma."*

So, the features the subject of the non-infringement case were held not to be part of the inventive concept and, as a result, infringement was found by equivalents. The concentration of the buffer solution (the solution being required to maintain a constant level of acidity, which affects coagulation) could apparently have been anything, despite the precision with which it was specified in the claim. And any thixotropic gel could be used, notwithstanding that the claim specified a polyester-based gel.

In the end, one does not know how HHJ Hacon arrived at his conclusion as to what the inventive concept – or "clever bit" – was. To borrow the Judge's own words (at paragraph 223) about the third *Actavis* question, *"it is not legitimate just to disregard an integer of a claim without further reasoning."* Yet (aside from referring to identification of the "clever bit"), that appears to be just what the Judge did when identifying the inventive concept and indeed answering the third question.

5.3 Technetix v Teleste [2019] EWHC 126 (IPEC)

The patent[32] concerned "tap units" that are used to reduce the strength of signals (provided to sophisticated junction boxes) and divide them for individual subscribers of cable TV or internet services. The Judge focused on cable TV in the Judgment. At trial, claim 1, which concerned a modular system that allowed a "directional coupler" to be replaced (so avoiding on site repair), was divided up into seven integers. On a normal construction, the alleged infringement did not have integers (2) and (4) (paragraph 107). So, the Judge went on to consider infringement by equivalents.

At paragraph 116, in finding that the inventive concept was integer (7), the Judge (HHJ Hacon) held:

> *"It was common ground that claim 1, if valid at all, depended on integer (7) for its validity. Integer (7) set out the new technical insight, if there was one."*

The Judge had already found that claim 1 lacked novelty over the cited prior art (paragraphs 63 and 78). In the alternative (on assumptions favourable to Technetix, the patentee), it was held to lack inventive step over the same prior art (paragraphs 64/70 and 79/83). So, one is forced to conclude that the Judge was equating inventive concept with inventive step (if any). That is consistent with what the same Judge had said in *Regen* where he referred to "the clever bit".

It would appear to follow that at least this Judge (HHJ Hacon) does not believe that inventive concept is used in the same way for the *Pozzoli* test and for Question i) of *Actavis*. In *VPG Systems v Air Weigh [2015] EWHC 1862 (IPEC)*, the same Judge, when addressing inventive step, held at paragraph 33:

> *"The inventive concept is not the same thing as the inventive step."*

And, as can be seen from the quote at the beginning of section 4.2 above, this has to be correct for the Pozzoli test to work.

In this respect, it is unfortunate that in *Technetix*, although the Judge referred to *Pozzoli* in his Judgment (paragraph 54), he did not go on and set out the analysis. Had he done so, this difference in approach would have come to light. As it is, one is left with an equivalency test that, for unexplained reasons, appears to depend on the relevant claim's inventiveness.

Before leaving this case, mention too should be made of the Judge's views on integers not within the inventive concept (paragraphs 110-1).

> *"I do not accept ... that a patentee must always go through each integer of his claim and the corresponding features of the accused product or process, and wherever an integer of the claim is missing from the accused product or process (or arguably missing), identify its equivalent. ...*
>
> *All integers of a claim missing from the variant will be relevant to, for instance, whether the inventive concept has been exploited by the variant in substantially the same way to achieve substantially the same result. No integer can be ignored. ... "*

In the author's view, the above statements are hard to reconcile. On the one hand, the Judge states, in effect, that there can be inessential integers but then, on the other hand, he states that no integer can be ignored. If integers are carved out of the claim as not being part of the inventive concept, how is it that they (or corresponding features of the alleged infringement, if any) can impact on that inventive concept?

5.4 Marflow Engineering v Cassellie [2019] EWHC 410 (IPEC)

The patent[33] was for a method of installing a fluid using appliance, such as a shower, on a wall. The pipework passed through a "mounting member", or plate, on the outside face of the wall. Claim 1 was split up into eight integers at trial. There were two infringement arguments, which respectively concerned integers (a)/(h) and (e)/(g).

Integer (a) called for "a part of a fluid pipe extend[ing] outwardly of the wall" and (h) for "joining the outwardly extending pipe part to an inlet fitting of the appliance". Relevant here is paragraph 17 of the Judgment, where the Judge recited one of the disadvantages given in the patent of a prior art arrangement:

> *"After the pipe parts and integral fittings have been joined, and the mounting plate is secured relative to the wall, the joint is inaccessible."*

In other words, in those arrangements, there was a pipe joint behind the wall after installation.

Integers (e) and (g) concerned the way in which the plate on the outside of the wall (referred to in the italicised quote in the paragraph above), though which the pipes passed, is locked to those pipes. Those integers called for "tightening a locking element", which is on "a locking member", itself in or on the plate. Importantly here, the plate "provid[es] in or thereon, a locking member".

The Judge explained (paragraphs 25-6; 30) the points at issue on infringement:

- *"First, the water pipes in the wall are not connected directly to the inlets of the shower or other appliance. They terminate inside the wall and are connected to what I will call an 'intermediary pipe'. The intermediary pipe passes from the pipe in the wall, through the mounting member or plate, to the shower inlet to which it is attached." (25.)*
- *"Secondly, the intermediary pipe has a screw thread on its periphery. It is fixed to the plate using one nut each side of the plate. The nuts are rotated on the screw thread of the intermediary pipe until they abut opposing sides of the plate, locking the intermediary pipe into a fixed position relative to the plate." (26.) And so, "[t]he issue is whether [the locking member] must be attached to the mounting member or whether it can be attached elsewhere." (30.)*

[31] European Patent (UK) 2,073,862.
[32] UK Patent No. 2,382,473.
[33] UK Patent No. 2,368,888.

On a normal construction, the Judge found (paragraph 29) that, in the alleged infringement, *"its intermediary pipe becomes a section of the fluid pipe within the meaning of claim 1"*. In relation to the locking feature, he found (paragraph 38):

> *"the locking member must be attached to the plate or form an integral part of the plate".*

Having found that, on a normal construction, the alleged infringement did not have the latter feature (paragraph 58), the Judge went onto consider equivalents.

In considering equivalents (in relation to the locking feature), although the Judge referred (at paragraph 55) to his Judgment in *Regen*, he now adopted a different approach to identification of the inventive concept. There is no reference in *Marflow* to "the clever bit". Instead, the Judge looked to the specification for guidance and concluded that the particular locking means was not part of it. At paragraph 61, the inventive concept was held to be:

> *"The idea of using a plate (mounting member) to install a fluid-using appliance by securing the plate to the wall, receiving the fluid pipes extending out of the wall through apertures in the plate and then using a locking means to lock the pipes in the plate."*

Importantly, note the absence of the words "in or thereon", which were present in the claim. In that regard, the Court noted (paragraph 62) that the specification contemplated different locking means to that exemplified in the specification (though not necessarily different from that claimed). That approach (of looking to the specification) is at least more in keeping with that adopted in *Markem* and *Pozzoli*. The Court also found that the infringing variant achieved the same advantages as the inventive concept (paragraphs 63-69).

However, by treating integers (a)/(h) in the manner that he did, the Judge glossed over an important point. The different locking means used in the alleged infringement required threaded pipework. As a practical matter, that mandated the infringement having an "intermediary pipe" and a joint behind the wall to connect with the fluid pipe. And that was one of the disadvantages that the patent sought to avoid. Because of the locking means used, the infringement had, and had to have, a joint behind the wall (whether or not there were unrelated joints elsewhere in the pipework, the possibility of which influenced the Judge's approach to integers (a)/(h) – see paragraph 29).

The inherent feature of integers (a) and (h) described earlier (no inaccessible joint behind the wall) should not, in the author's view, have been disassociated from integers (e) and (g). In rebuttal, it might be said that the feature was well known and acknowledged as such in the patent (Judgment, paragraph 18). However, this case would be a perfect example as to why salami slicing a claim, and removing those slices which are CGK to identify an inventive concept, simply cannot be right. This patent was all about a combination of features.

Further, it is unfortunate that again, although the Judge referred to *Pozzoli* when addressing the inventive step attack on the patent (paragraph 41), he did not set out the analysis and identify an inventive concept for that purpose. Had he done so, and relied on the *Pozzoli* guidance set out earlier, a different result on infringement may well have followed.

5.5 Eli Lilly v Genentech [2019] EWHC 387 (Pat)

Of this case, Arnold, J. stated in his Judgment (paragraph 3):

> *"this is one of the most complex patent cases I have ever tried".*

However, there is no need for a summary of the relevant claim and facts of the case because the Judge did not need to find infringement by application of the doctrine of equivalents. Consequently, he only briefly considered the *Actavis* questions in case he was wrong on a normal construction.

In dealing with Question i), the Judge asked himself *"does the variant achieve substantially the same result in substantially the same way as the invention?"* In this case, the variant feature was an antibody that was, not only specific to a particular molecule referred to in the claim (IL-17A/F), but also to another allied molecule (IL-17A/A). He concluded that the answer to the question was yes, but the Judge did not, as part of that exercise, seek to identify an inventive concept. (See paragraph 598(i).) The Judge seems to have viewed the inventive concept as simply being what was in the claim.

With regard to third Actavis question (at paragraph 598(iii)), the Judge appeared to be willing to go back to the specification (including the description) to check what the patentee was saying – i.e., whether specificity to an additional molecule was ruled out. He held *"that there is nothing in the Patent to indicate that the antibodies should bind to IL-17A/F only when used for therapeutic purposes."* Contrast that with the approach in *Icescape* referred to earlier.

6. CURTAILMENT

In other jurisdictions where there is a doctrine of equivalents, constraints have been put on its application through one or both of: prosecution history (file wrapper) estoppel; and a defence of practising the prior art.

What of the UK? Given the approach in some of the cases discussed above to determine the inventive concept, there is clearly a need for some curtailment. However, in the UK, the prosecution history, and practising the prior art, defences have themselves been curtailed.

6.1 Prosecution history

Lord Hoffman's view about reviewing the prosecution history, expressed in *Kirin-Amgen* (paragraph 35), was that *"life is too short for the limited assistance which it can provide."* In Actavis, Lord Neuberger appeared to have toned that attitude down, saying at paragraph 87 that:

"In my judgment, it is appropriate for the UK courts to adopt a sceptical, but not absolutist, attitude to a suggestion that the contents of the prosecution file of a patent should be referred to when considering a question of interpretation or infringement, along substantially the same lines as the German and Dutch courts."

In paragraph 88, he went onto identify two non-exhaustive circumstances where it might be appropriate to refer to the prosecution history:

> *"(i) the point at issue is truly unclear if one confines oneself to the specification and claims of the patent, and the contents of the file unambiguously resolve the point, or (ii) it would be contrary to the public interest for the contents of the file to be ignored."*

On the facts in *Actavis*, the prosecution history was held not to assist the alleged infringer. Lord Neuberger stated (paragraph 89):

> *"It seems to me clear that the reason why the examiner considered that the claims in the patent should be limited to pemetrexed disodium was because the teaching in the specification did not expressly extend to any other anti-folates. ... even if the examiner was right or at least justified in taking the stance that he did, I do not consider that that consideration can have any bearing on the question whether any pemetrexed salts other than pemetrexed disodium should be within the scope of the patent pursuant to the doctrine of equivalents."*

Lord Neuberger does not explain why it wasn't, on the facts, in the public interest to limit the application of the doctrine of equivalents in *Actavis*. Perhaps it reflected a general concern that the examination process does not involve all the enquiries that are made at a full-blown patent trial. Or perhaps it was the nature of the Examiner's objection. Would a lack of patentability over cited prior art be treated differently?

Prosecution history estoppel came up in *Icescape*, where the relevant amendment had been made in response to a lack of novelty objection. At paragraph 79, Lord Kitchin dismissed reliance on prosecution history estoppel for three reasons.

First, he found it impossible to determine whether the objection raised by the Examiner that led to the relevant amendment was a sound one. Second, he found it impossible to determine whether the relevant amendment was necessary to meet the Examiner's objection. Third:

> *"More importantly, it is impossible to discern in the correspondence any suggestion that Ice-World was surrendering an ability to argue that features D and E were inessential or that Ice-World was accepting that the scope of the claims did not extend to a system in which the feed and discharge manifolds were connected in parallel rather than in series." (A series connection followed from the arrangement of features D and E – see earlier.)*

The upshot of this decision, particularly the quoted passage above, is that the "life is too short" view appears still to be prevalent, though the door has not been shut altogether on prosecution history estoppel.

Note too here the reference to "inessential" features in the quoted passage above. This is consistent with the Court of Appeal's approach of not seriously trying to find features equivalent/corresponding to integers of the claim, but rather simply ignoring those integers that are not part of the inventive concept. That approach is reflected in other cases referred to above (for example, ignoring the sodium citrate concentration in *Regen*).

Lord Neuberger may have thought that *Actavis* was not a substantial departure from the old law, but disregarding integers is such a departure. Admittedly made before *Kirin-Amgen* (and indeed *Improver*, both of which owe their origins to the older case of *Catnic*[34]) the following quote would have held good prior to *Actavis*: "where it is a question of totally disregarding an explicit feature of a claim, such cases have been extremely rare."[35]

Returning to prosecution history, the point came up again in *Regen*. In distinguishing Smith, cited by the EPO Examiner, Regen's patent attorneys wrote (letter dated 31 May 2013; Judgment, paragraph 254):

> *"Hence for each tube, a specific combination of a particular tube's material, particular thixotropic gel and particular anticoagulant is claimed. In addition, depending on the tube used, the anticoagulant is to be present in a specific state (solution or anhydrous) and at a specific concentration.*
>
> *...*
>
> *In summary, the primary feature of the processes which distinguishes them from those disclosed in [Smith] is the use of specific tubes."*

The anticoagulant referred to is sodium citrate (Judgment, paragraph 58). Claim 1 called for a concentration (molarity) of 0.10M. It also called for a polyester thixotropic gel.

The Judge dismissed the prosecution history argument at paragraph 255:

> *"I think that the letter of 31 May 2013 satisfies neither requirement specified by Lord Neuberger. There is no issue of construction or scope which is truly unclear if one confines oneself to the specification and claims of the patent, for the reasons discussed above. Nor would it be contrary to the public interest for the letter to be ignored. Regen argued before the EPO that the scope of the claim they were advancing did not overlap the disclosure of Smith. It does not. That is consistent with Regen's argument on scope before me."*

So, although Regen relied on its claimed specific combination of features to distinguish Smith, that was not sufficient to tie it down to the specific integers of sodium citrate concentration and type of thixotropic gel within that combination when asserting infringement. The basis for that conclusion is said to be that the claim does not overlap with Smith since the latter does not disclose the claimed combination. However, when identifying the inventive concept, the Judge effectively ignored several of the features of the claimed combination. Whether in accordance with *Actavis* or not, the difference in treatment of the claimed combination when identifying an inventive concept and applying prosecution history estoppel is striking.

6.2 Practising the prior art (Gillette/Formstein/ensnarement)

With regard to a defence of practising the prior art, well before *Actavis* the UK Courts had, from time to time, acknowledged the so-called *Gillette* Defence. That traces its origins to Lord Moulton's speech in *Gillette Safety Razor v Anglo-American Trading (1913) 30 RPC 465*, at page 480:

> *"But he is entitled to feel secure if he knows that which he is doing differs from that which has been done of old only in non-patentable variations such as the substitution of mechanical equivalents or changes of material, shape or size. The defence that 'the alleged infringement was not novel at the date of the Plaintiff's letters patent,' is a good defence in law ...".*

Commentators have questioned if it is really a separate defence.[36] The point is that it is only a defence in that there can be no infringement of an invalid patent – i.e., it is not a free-standing defence. Perhaps for that reason, one commentator referred to it as a short cut.[37] In *Gillette* itself, the defence was not applied, the patent being held valid but not infringed. And, in *Fujifilm v Abbvie Biotechnology [2017] EWCA Civ 1* at paragraph 56, the Court of Appeal recently preferred to see infringement and validity as being decided separately and referred to the "defence" both as a short cut and a cross-check.

There is *now* another way that the Court could approach this defence. As described earlier, in an inventive step attack in the UK, the Courts will often apply the *Pozzoli* test and that test requires the identification of an inventive concept. On the assumption that the inventive concept is to be ascertained in the same manner for the *Pozzoli* inventive step test and the *Actavis* equivalency test, then there could be a defence as follows. If the patentee has to cast his inventive concept so broadly to catch the alleged infringement by equivalents that the patent fails the fourth stage of the *Pozzoli* inventive step test, then there would be no infringement. And that defence would not require a finding of invalidity. (That would depend upon what the inventive concept was actually found to be.) Indeed, viewing inventive concept as a potential vehicle for such a defence provides a compelling reason for the *Actavis* inventive concept to be the same as that in *Pozzoli*.

[34] Catnic v Hill & Smith, House of Lords, [1982] RPC 183.
[35] Patents for Inventions, Blanco White, 5th edn. at 2-111.
[36] E.g., Terrell, 18th edn, 14-266.
[37] Patents for Inventions, Blanco White, 5th edn. has it under a heading of "short cuts" at 4-208.[38] Decision of the FCJ (April 29, 1986 - X ZR 28/85 – Formstein; "Formsteinneinwand"), reported in English at [1991] RPC 597."short cuts" at 4-208.
[39] Ibid.
[40] www.supremecourt.
[41] See Conroy v. Reebok Intern., Ltd., 14 F.3d 1570, 1576-77 (Fed. Cir. 1994).
[42] Biogen v Medeva [1997] RPC 1.

One question to resolve for such a defence based on inventive concept would be on whom the burden of proof would fall to show respectively that the *Pozzoli* test was passed or failed. That matter is a point of distinction between the German *Formstein*[38] and US ensnarement defences discussed next.

The Judge in *Technetix* considered the above type of defences at paragraphs 85-101 and 126-133. He specifically referred to *Formstein* and ensnarement and considered that the UK Supreme Court or the Court of Appeal might, at some time in the future, introduce a *Formstein* defence (at paragraph 99). At paragraph 133, he found that "if a Formstein defence exists in English law, *Teleste is entitled to the defence.*"

Note that, as the author understands it, the *Formstein* defence, which provides a defence of practising the prior art, or what was obvious over it, is only available in the German infringement Courts as a defence to infringement by equivalents. Were it otherwise, the infringement Court would be adjudicating on validity over which it does not have jurisdiction. This point also reflects the distinction drawn between claim scope (validity) and extent of protection (infringement).

In relation to burden of proof, it is clear that, under German law, the alleged infringer must make out the defence. See *Formstein* itself at page 606[39] and the FCJ (or BGH) decision of 17. 2.1999 - X ZR 22/97 (at paragraph I.4(f)).

By contrast, the US ensnarement defence puts the burden on the patentee (see *Jang*, referred to below, at page 15). If ensnarement is raised, the patentee will often produce hypothetical claims that it asserts would cover the alleged infringement but are not disclosed by the prior art or obvious over it. Such hypothetical claims are not allowed to introduce new limitations (to avoid the prior art). It is then for the patentee to show that the claims are patentable over the relevant prior art

The difficulty for a patentee in dealing with the hypothetical claim ensnarement rules is illustrated by *Jang v. Boston Scientific Corp. & Scimed Life Systems Inc., No. 16-1275 (Fed. Cir. Sept. 29, 2017)*. The patentee was ultimately unable to produce the requisite claims and his frustration was evident in the unsuccessful documentation petitioning the US Supreme Court in which the patentee described the rules as "Byzantine".[40]

Apart from the burden of proof difference with *Formstein*, the hypothetical claim approach (where new claims are expressed to take account of equivalents) also gives the alleged infringer a broader defence. The defence is available if a different equivalent from the alleged infringement is not new and/or inventive over the relevant prior art. The more broadly the hypothetical claims are cast, the greater the risk of encompassing the prior art. However, *Jang* confirmed (at footnote 4) that another approach would be to ask if the alleged infringement would itself have been obvious over the prior art.[41] Nonetheless, the hypothetical claim approach appears to be the preferred method for the ensnarement defence analysis. See *Wilson Sporting Goods Co. v. David Geoffrey & Associates 904 F.2d 677 (Fed. Cir. 1990)* at 684.

There is a logical attraction to the US hypothetical claim approach in that it gives the broader defence described above. If the scope of such a claim, as a consequence of covering the infringement, must also cover other equivalents that are not patentable over the prior art, why shouldn't there be a defence? Further, as it is the patentee who is asserting infringement and that the patent should be afforded broader protection, why shouldn't the onus be on the patentee to show that such a hypothetical claim would have been patentable with respect to the prior art? However, the only judicial indication to date is that the UK Courts might consider a *Formstein*-type defence. And the dos and don'ts of hypothetical claim drafting might prove to be cumbersome and time-consuming when compared with the *Formstein* approach.

Before leaving this topic, insufficiency merits a mention. It is possible that, using the hypothetical claim approach (or the inventive concept approach), an argument might be developed that a defence should be available because the hypothetical claim (or broadly cast inventive concept) was not enabled across its breadth. The point is not developed further in this article, not least because this "*Biogen*[42] insufficiency" could easily be the subject of a paper on its own. (That would include *Lundbeck*, discussed above.)

7. IMPACT ON INTERIM INJUNCTIONS, "CLEARING THE WAY" AND ARROW' DECLARATIONS

In the UK, generic pharmaceutical companies are well advised "to clear the way" – i.e., seek a declaration of non-infringement and/or revoke the relevant patent prior to launch. Failure to do so may substantially increase the risk of an interim injunction. See paragraphs 38-40 of *SKB v Apotex [2003] EWCA Civ 137* - at paragraph 40:

> *"The Judge was, in my view entitled to take into account when deciding to maintain the status quo that Apotex walked into the situation that they find themselves in with their eyes open to the risk that they were taking."*

However, clearing the way may not be as straightforward as starting one set of proceedings. The EPC allows for the filing of divisional applications provided that an application, including a divisional application, is pending. "Cascading divisionals" can be filed several years after the original application, but still retain the original priority date. As a consequence, competitors may be unable to determine the extent of patent protection that may exist in the future over a specific product or process that it wishes to launch/use. This has proven to be a significant issue in the pharmaceutical sector.

In order to allow potential competitors to obtain commercial certainty (in the above circumstances), the UK Courts are prepared to grant a declaration that a particular product or process was not new or was obvious at the relevant priority date. *Fuji* (referred to earlier)[43] confirmed the availability in English law of these "*Arrow* declarations".[44] Interestingly, the author understands that they may well not be available in Germany, it not being clear which Court in a bifurcated system would/could grant such a declaration.

With the advent of a UK doctrine of equivalents, one can see how *Arrow* declarations may become of increasing importance with regard to clearing the way for generic pharmaceutical companies. The potential problem of cascading divisionals has now been compounded by the uncertainty that accompanies a doctrine of equivalents, particularly one relying on the identification of an inventive concept in the manner described in some of the cases above.

8. CONCLUDING REMARKS AND THE FUTURE

These are relatively early days for the UK Courts with respect to applying the *Actavis* equivalents test. However, in the author's view, in some of the cases described above, the Courts have:

- *been too willing – indeed eager – to ignore claim integers altogether (inessential integers);*
- *paid too little attention to what the patentee says in the specification is the invention (c.f., Pozzoli and Markem); and*
- *unjustifiably assessed inventive concepts by reference to some or all of the relevant state of the art (again, c.f., Pozzoli and Markem) and thereby, for example, ignored features, seemingly CGK when viewed in isolation, which contributed to the inventive concept.*

Lord Neuberger clearly did not intend or think that Actavis would have the profound effect that it has by substantially relegating the status of patent claims. Moreover, the balance required by Article 1 of the Protocol to EPC, Article 69 has clearly been shifted in the UK in the direction of legal uncertainty. Parties and their advisors are being left to distil some generalised (though perhaps not amorphous) idea of what the extent of a patent's protection might be.

On the other hand, in the more recent *Marflow* and *Eli Lilly cases*, the exercise of identifying broad inventive concepts by reference to the state of the art was not conducted. And, the judicial acknowledgement that a *Formstein* defence might exist in the UK has to be viewed as a welcome indication that the doctrine of equivalents will be constrained in some manner so as to achieve equitable results.

[43] Fujifilm Kyowa Kirin Biologics Co, Ltd v AbbVie Biotechnology Ltd & Another [2017] EWCA Civ 1.

[44] Named after Arrow v Merck [2007] FSR 39.

[45] The Judge in BDI even referred (paragraph 27) to his Judgment in Regen, seemingly as illustrative of his finding at paragraph 21 about usage of the phrase in the three contexts of entitlement, inventive step and equivalents.

[46] The Judge held (in relation to unity; paragraph 28) that "Those who drafted art.82 and rule 44 EPC had in mind a 'general inventive concept' which is not similar to the inventive concept contemplated by the House of Lords in Yeda." For reasons already explained, the author concurs that unity has its own definition but would not have chosen to compare it with the explanation of "inventive concept" given by Lord Hoffmann in Yeda.

[47] That inference is reinforced by paragraph 40, where the Judge held that "... where both sides' witnesses stated that some technical matter would be known to the skilled person, I have treated it as an agreed fact."

9. POSTSCRIPT

After the author finished writing the article above, HHJ Hacon gave Judgment in an entitlement case, *BDI v Argent [2019] EWHC 765 (IPEC)*. If it wasn't clear enough already, it should be in the light of that case that the issue of how to identify an inventive concept needs to be considered urgently by the Court of Appeal or Supreme Court. It is nonetheless appropriate to point out, at this juncture, that it is the arguments put before the Judge by the parties' representatives that shape a Judgment. In this postscript, the author has confined himself to making two points.

First, in *BDI*, the different contexts in which the phrase "inventive concept" arises was discussed. The Judge held (in relation to entitlement, equivalents and inventive step; paragraph 21) that *"If the meaning given to 'inventive concept' differs at all as between Yeda, Actavis and Pozzoli, it is not by much."* In the author's view, this misses the point. As discussed above, the phrase *should* have the *identical* meaning for these three purposes but it is clear that the Courts in *Icescape, Regen*[45] and *Technetix* have not applied the same test for equivalents as set out in *Pozzoli*. The Judge did, however (and correctly, in the author's view), consider the use of the phrase in unity as a special case.[46]

Second, the Judge in *BDI* also referred (paragraph 33) to *Markem* because: each party asserted that the inventive concept contended for by the other was not inventive; and in *Markem*, Jacob, L.J. had held (paragraph 88) that, when there is a self-evidently and unarguably invalid monopoly being claimed, the Court should take that matter into account when exercising its wide discretion to remove an invalid monopoly. Although it is not wholly clear, this may have led the Judge in *BDI* to conclude (paragraphs 38-9) that, had there been expert evidence before him, he would have: taken the relevant CGK into account (i.e., presumably, stripping it out, as in *Icescape*); and, more generally, considered what may have been obvious, in order to identify the inventive concept. This, in the author's view, is clearly not what Jacob, L.J. had in mind in paragraph 88 of *Markem* as the correct approach for identifying an inventive concept (see too the quote in Section 4.3 above from paragraph 103).

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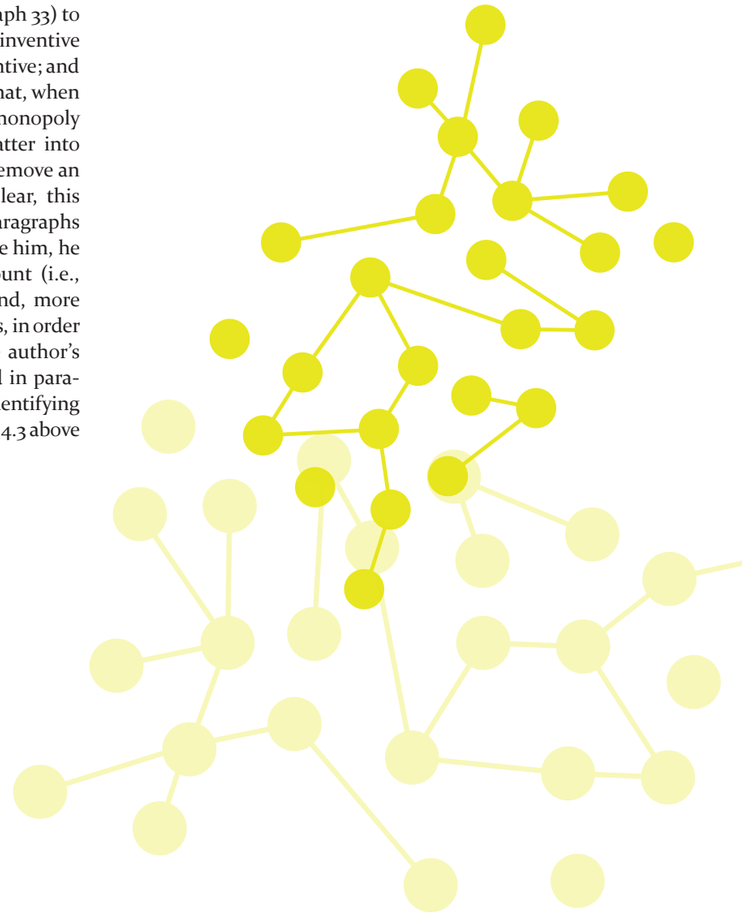

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Second medical use claims and scope of protection

- A work in progress since 1984

By Clara Berrisch

ABSTRACT

Second medical use patents and their claims do not only represent highly valuable inventions for both originator and generic pharmaceutical companies, but have also been a topic of debate for many years. In particular, this is due to the fact that these inventions were originally not patentable under the European Patent Convention (EPC) in 1973 and thus required a special claim formulation, known as a Swiss-type claim. The later codification of this judge-made law in the course of the revision of the EPC in the year 2000 resulted in a different claim formulation, referred to as EPC 2000 claims. Since then, the impact of these different formulations on the respective scopes of protection conferred by both claim types has been a source of controversy and as such, much discussed. More recently, with the rise of the European-wide patent litigation surrounding Warner-Lambert's patent for a substance marketed as Lyrica®, second medical use claims have also been a hot topic when it comes to infringement. The national courts, which are responsible for the enforcement of patent law in Europe, have thus been faced with the question of the scope of protection conferred by second medical use claims. Concurrently, through their decisions, the national courts also shape the scope of protection.

This article's main focus is how second medical use claims and especially their scopes of protection have developed throughout the years. It will firstly provide a short background on the importance of second medical use inventions and the necessity to allow their patentability. Following this, it will outline the origin of both Swiss-type and EPC 2000 claims while focussing on the differences in their respective scope of protection. Lastly, it will analyse the recent developments in German case law on patent infringement, as well as their impact on the scope of protection of second medical use claims.

1. THE IMPORTANCE OF SECOND MEDICAL USE PATENTS

Second medical indications occur in a number of situations. The case may be that a drug is placed on the market for a first indication and it is discovered through this use that it is also beneficial for the treatment of other illnesses; hence, if a patient has two illnesses and the drug indicated for one of these has a positive effect on both illnesses. It could also simply be that research is continued on the drug for other therapeutic indications even after it is placed on the market for a first medical indication.[1] Such 'drug repurposing' is a common business strategy employed by pharmaceutical companies to expand the life cycle of a product.[2] However, further research is also conducted when a target[3] is relevant for two indications. In that case, the pharmaceutical company will aim to place the product on the market as soon as they discover positive effects on one indication, in order to be the first ones to enter the market, while still continuing research regarding the second and further indications. Second medical indications can also occur when a first known use is not successful.[4] It is also imaginable that compounds known for non-medical uses are later discovered to be effective for medical uses, as is the case for e.g. the medicinal use of marijuana.[5]

These patents may sometimes be wrongfully perceived as weak patents because the scientific progress may seem minimal to an outside observer due to the abundance of publications concerning the (already known) substance.[6] However, from an economic perspective, they are valuable inventions that often entail high costs.[7] As the tolerance and side effect profile of these inventions is typically already known from the first indication product, second medical use products are highly beneficial for patients.[8] This is the reason why there was a general need in the sector to allow patentability of second medical use inventions in order to promote R&D of such medications.

2. CLAIM CONSTRUCTION OF SECOND MEDICAL USE CLAIMS

As mentioned, second medical use claims and their formulation have come a long way. To assess the differences in the scopes of protection of both Swiss-type and EPC 2000 claims, it is necessary to understand the purpose and origin of the two claim types.

2.1. Swiss-type claims

Swiss-type claims were developed by the Enlarged Board of Appeal (EBA) of the European Patent Office (EPO) in a landmark decision, G 5/83 *(Second medical indication/EISAI)*.[9] This decision circumvented certain patentability exclusions contained in the EPC 1973, which made patenting of second medical use inventions impossible. In doing so, the EBA adopted the practice of the Swiss Federal Intellectual Property Office,[10] according to which second medical use inventions could be protected by a purpose-bound method claim. This claim took the form 'use of a substance or composition for the manufacture of a medicament for a specified (new) therapeutic application' and was referred to as a Swiss-type claim.[11]

The decision of the EBA in G 5/83 was highly controversial and encountered criticism in particular regarding the 'fundamental legitimacy' of Swiss-type claims.[12] Another main point of criticism was that the solution was ill-conceived and did not consider the further implications of this claim format in infringement proceedings. It cannot be denied that the solution reached in G 5/83 was suboptimal and could not have been intended as a permanent solution. It was an attempt to fit a rule that was intended otherwise to the necessities and demands of the industry.

Prior to this, the German Federal Court of Justice (the Bundesgerichtshof, BGH) developed its own approach to patenting second medical use inventions. In its *Hydropyridine* resolution[13], it concluded that second medical use inventions should be protected through use claims and argued that the subject-matter of such a claim did not only contain the treatment of the illness in question but also the 'manifest arrangement'. The concept of 'manifest arrangement', which is translated from the German term *'augenfällige Herrichtung'* or *'sinnfällige Herrichtung'* means the arrangement of a medicament for a specific use.[14]

2.2. EPC 2000 claims

After judge-made law temporarily solved the issue concerning the patentability of second medical use claims, the reformation of the EPC in the year 2000 came as an opportunity for a more permanent, legislative solution.

A common denominator of all reformation proposals was to provide legal certainty both for the national courts and for those affected by the law. Finally, the EPC drafters agreed to amend Art. 54(5) EPC so that it allowed the patentability of second medical use inventions provided their use is novel and they fulfilled the additional patentability criteria. To differentiate them from Swiss-type claims, claims granting second medical use patents in accordance with Art. 54(5) EPC 2000 are referred to as EPC 2000 claims. These claims take the (much simpler) format: 'Substance X for use in the treatment of condition Y' and are purpose-bound product claims.[15]

2.3. The scope of protection of both claim types

The scope of protection of a claim is the crux for the strength of the patent. It is closely interlinked with the infringement of that claim. A patent holder can only enforce the patent and take action against any possible infringers as far as the patent holder enjoys protection. Determining the scope of protection is therefore necessary to provide legal certainty for the following three parties: first, for the patent holder who needs to know what the exclusive right encompasses and what he can prohibit competitors to do; second, for the competitors, who in turn needs to know what they can do and which actions constitute infringement; last, a clear determination of the scope of protection benefits the national courts since they have the exclusive jurisdiction regarding patent infringement.[16] It should also be kept in mind that legal certainty about the scope of protection of a claim benefits the industry as a whole, because this will minimise the risks.[17] Taking the perspective of an innovator pharmaceutical company as an example, it can be assumed that a company is more likely to invest in the costly R&D of a second medical indication medicament, if it feels confident about the scope of the legal protection concerning this medicament.

1 Mitali Bhagwat, Geetesh Kaushik and Vijaykumar Shivpuje, 'Second Medical Use Patenting: A Review of Practices Across Different Jurisdictions' (2016) 21 JIPR 260, 262.
2 Ibid 261.
3 "Target" can be defined as the naturally existing cellular or molecular structure involved in the pathology of interest that the drug-in-development is meant to act on.
4 Bhagwat, Kaushik and Shivpuje (n 1) 260.
5 Ibid 262.
6 Andreas von Falck and Miriam Gundt, 'Die Verletzung von Ansprüchen auf die zweite medizinische Indikation' in Thomas Kühnen (ed), Festschrift 80 Jahre Patentgerichtsbarkeit in Düsseldorf (Carl Heymanns Verlag 2016) 113, 114.
7 Frank-Erich Hufnagel, 'Der Schutzbereich von Second Medical Use Patenten' (2014) 2 GRUR 123.
8 Ibid.
9 Case G 5/83 Second medical indication/EISAI [1984], ECLI:EP:BA:1984:G000583.19841205.
10 Included in the Swiss legal advice of 30 May 1984, cf Jürgen Meier, 'European Patent Office' in Jochen Bühling (ed), Patent Protection for Second Medical Uses (Wolters Kluwer 2016), 9.
11 Case G 5/83 [19].
12 Matthew Fisher, 'Second medical indications and the Swiss-form claim: taming Frankenstein's monster: Part 1 – solving one problem creates another' (2017) 39 EIPR 574, 575, with reference to inter alia Julian Cockbain and Sigrid Sterckx, 'Is the Enlarged Board of Appeal of the European Patent Office Authorised to Extend the Bounds of the Patentable? – The G-5/83 Second Medical Indication/EISAI and G-2/08 Dosage Regime/ABBOT RESPIRATORY Cases' (2011) 42 IIC 257, 271.
13 BGH NJW 1984, 663.
14 This concept will be explained in Section 3.1.1 below.
15 Meier (n 10) 10-11.
16 Jochen Bühling, 'Germany' in Jochen Bühling (ed), Patent Protection for Second Medical Uses (Wolters Kluwer 2016), 35, 49.
17 Matthew Fisher, 'Second medical indications and the Swiss-form claim: taming Frankenstein's monster: Part 3 – the Franken-cuckoo comes home to roost' (2017) 39 EIPR 705, 706.

The scope of protection of both Swiss-type and EPC 2000 claims has been the topic of many discussions in the preparatory works of the EPC, but has also kept courts and researchers busy after the latter came into force in 2007.[18] The main issue is that there is a discrepancy between the reasoning behind EPC 2000 claims and the de *facto* legal effect of these claims. They were introduced as a codification of the jurisprudence at the time (that had created Swiss-type claims), however, as they pertain to a different claim category than Swiss-type claims it is impossible for them to have the same scope of protection.

First and foremost, the scope of protection conferred by a claim is determined by the respective claim itself,[19] and thus by its category. There are two categories of claims,[20] which correspond to the two categories of inventions, namely method/process claims on the one hand and product claims on the other. The difference lies in the fact that methods and processes are intangible, whilst products are tangible. As seen above, Swiss-type claims are (purpose-related) process claims and EPC 2000 claims are (purpose-related) product claims. This means that they are governed by different sections of the national patent legislation, which has consequences not only for their scope but also when it comes to infringement.[21]

Initially, both claim types co-existed and could even be combined in the same application. However, in 2010, the EBA of the EPO put an end to Swiss-type claims in their landmark decision G 2/08 *(Dosage Regime/ABBOT RESPIRATORY)*.[22] The board held that, following a transition period of three months after publication of the decision, second medical indication patents could only be applied for in the format provided in Art. 54(5) EPC.[23] The reasoning behind this was that Swiss-type claims had been invented to remedy a loophole in the EPC 1973, which has now been closed by the new provision of the EPC. As a result, the construct of Swiss-type claims had become redundant, or as the EBA put it: 'when the reason of law ceases, the law itself ceases' *(cessante ratione legis, cessat et ipsa lex)*.[24] Of course, the existing patents with Swiss-type claims are still valid until expires out, which means that Swiss-type and EPC 2000 claims will continue to co-exist until January 2031, possibly even January 2036 if patent extensions due to Supplementary Protection Certificates (SPCs) are factored in.

After considering all these factors, it can be concluded that, despite the intention found in the *travaux préparatoires* to the EPC, Swiss-type and EPC 2000 claims pertain to different claim categories and thus necessarily have a different scope of protection. The scope conferred by EPC 2000 claims is slightly broader since these are product claims. This finding has been confirmed in numerous EPO court decisions.[25] While there is no record that this was borne in mind by the drafters of the EPC, it has to be assumed that their expertise would have enabled them to consider this consequence of choosing a different claim category. The newest developments in the German jurisprudence acknowledge this by assimilating the scope of protection, whereby both types confer the scope of protection as provided by the EPC 2000.[26] It should also be noted that by extending the scope of protection, the situation for originator companies, which are typically the holders of second medical use patents, has improved rather than worsened. Therefore, this development is seen as 'patent holder friendly.'[27] On the other hand, it should not be forgotten that while originator companies are mainly in competition with generic companies when it comes to second medical use patents, they also compete with other originator companies.[28] As such, they are always at risk of being potential infringers and thus strengthening the rights of patent holders may not necessarily be as beneficial for patent holders as it seems at first sight.

3. INFRINGEMENT OF SECOND MEDICAL USE CLAIMS

The relation between Swiss-type and EPC 2000 claims manifests itself in infringement cases all over Europe, as a European patent granted for all EPC member states has to be enforced at national level.[29] The following section will provide an analysis of the consequences of these decisions for the relation of Swiss-type and EPC 2000 claims with regard to their respective scopes of protection on the basis of German case law.

3.1. Infringement of Swiss-type claims[30]

The underlying issue with all second medical use cases is that they require two rights to be balanced. On the one side, there is the right of the patent holder to a fair protection of the second medical use patent, and on the other side, the right of third companies to make use of the patent-free first indications, which goes hand in hand with the right of the general public to access cheaper, generic pharmaceuticals after the patent has expired.[31] After all, the concept of patent law is that an originator is granted exclusive rights for a specific period of time, but in return has to share the knowledge with society, which can then make use of it after that period has lapsed.[32] The problem here is that a use for the separate indications cannot be strictly separated. This is due to two regulatory law factors whose explanation requires a small excursus:

The first factor to take into account is the way medications are prescribed by physicians. Most prescriptions are written generically, meaning by reference to an active substance instead of a branded product.[33] In fact, the regulatory system for prescriptions in Germany encourages physicians to prescribe generically. Every prescription contains a box with the phrase aut idem, which translates to 'or the same'.[34] If the physician does not cross it, the pharmacist is obliged to substitute this product with any other version of the medicament with the same active ingredient that is identical to the prescribed product.[35] This means that the standard version of a prescription is designed to allow for substitution.[36] Additionally, physicians face a lot of pressure from health insurance companies to not cross out the aut idem-box to save costs,[37] and even risk to be investigated if they tend to prescribe branded products.[38]

The second factor is the substitution obligation to which pharmacists are subjected.[39] According to § 129(1) of the German Social Insurance Code, fifth Book (SGB V), when they are handed an aut idem or generic prescription, they are required to provide the least expensiv product (with the mentioned active ingredient in the mentioned composition) available.[40] In most cases, this will be a generic product.

3.1.1. Purpose-bound protection and manifest arrangement

The common basis of all decisions analysed for the purpose of this section is that they all emphasise the fact that the protection conferred by a second medical use claim is purpose-bound. This special phenomenon is called *Zweckbindung* in German, which would translate to 'purpose-boundness.' This is what makes the nature of a second medical use claim. This type of patent is not awarded for the use of a substance for the manufacture of a medicament but for the fact that this is done to either treat a specific illness or an illness in a specific way.[41] The purposeful use of the substance is what is inventive in these cases. This was also addressed in *Antivirusmittel*,[42] a decision by the BGH from 1987. In the judgement, the Federal Court of Justice held that the use of the patented subject-matter is excluded when the purpose is neither aimed at nor achieved in a targeted way.[43]

To sufficiently take this into account, the German courts have developed the concept of manifest arrangement as described earlier in this article. The idea behind this is that by manifestly arranging a product, it is given its purpose.[44] The need for this requisite lies in the nature of the second medical use – as the product can also be used in a non-infringing manner (for the patent-free first medical indication), the use of the product itself does not amount to an infringing behaviour. Infringement only occurs when the product is intended for use for the second medical indication. Thus, a purpose relation is necessary. Requiring the manifest arrangement of a product is a way for the courts to determine whether the potential infringer intends to use the product in the protected manner. Manifest arrangement can be seen in processes such as making into a confection ready-to-use preparation, but also in dosage or label instructions or other ways of arranging the product, when this is done with the purpose to use the product for the protected indication.[45] The following section will demonstrate how this requisite was adapted over time.

3.1.2. Skinny labelling as a 'Safe Harbour' – Ribavirin, Chronische Hepatitits C-Behandlung and Cistus incanus

The downside to having manifest arrangement as the main point of reference when finding infringement is that the latter can be avoided quite easily by the generic companies, who are the (potential) infringers in these cases. To put a generic drug on the market, they can apply for a marketing authorisation (MA) in a simplified application process, which allows references to the authorisation documents of the original pharmaceutical ('reference pharmaceutical').[46] This process allows the exclusion of certain patented indications from the summary of product characteristics (SmPC) and the package leaflet (PL).[47] This method is referred to as 'carve out' and the MA resulting from this process is then called a 'skinny label'.

18 See for example the following articles whose titles translate to "The Scope of Protection of Second Medical Use Patents": Hufnagel (n 7); Nina Schäffner, 'Der Schutzbereich von Second Medical Use Patenten II: Entwicklung im Lichte von "Lyrica", "Pemetrexed", "Östrogenblocker" und "Verwendungspatent"/"Glasfaser II"' (2018) 5 GRUR 449.

19 Lionel Bently and Brad Sherman, Intellectual Property Law (4th edn, OUP 2014), 627.

20 For the purpose of this study, the term "categories of claims" differentiate between process and product claims and is not to be confused with the term "types of claims", which differentiates between, inter alia, independent and dependent claims, cf Guidelines for Examination before the EPO, section F-IV, 3.1.

21 Frantzeska Papadopoulou, 'Construction and enforceability of Swiss-type claims: The myth lives on?' (2015) 5 NIR 479, 480.

22 Case G 2/08 Dosage Regime/ABBOT RESPIRATORY [2010], ECLI:EP:BA:2010:G000208.20100219.

23 Case G 2/08, Reasons 7.1.4.

24 Case G 2/08, Reasons 7.1.2.

25 The EPO touched on this subject in decisions concerning double patenting or post-grand amendments of the patent pursuant to Art. 123 EPC. A detailed study of these decisions is included in the original version of this thesis.

26 Armin Kühne, 'Verletzungshandlungen bei zweckgebundenem Stoffschutz' (2018) 5 GRUR 456, 456.

27 Matthias Zigann, 'Infringement of Swiss-Type Second Medical Use Patent Claims in Germany - Recent Developments in Case Law' (2017) 12 Wash. J.L. Tech. & Arts 245, 245.

28 Bühling (n 16) 38.

29 Sir Richard Arnold, 'An Overview of European Harmonization Measures in Intellectual Property Law' in Ansgar Ohly and Justine Pila (eds), The Europeanization of Intellectual Property Law (OUP 2013), 25, 27.

30 The vast majority of the relevant case law concerns second medical use patents with Swiss-type claims, which is simply due to the time it takes for a patent to be processed. However, this does not mean that they do not mention the relation between Swiss-type and EPC 2000 claims or that they are not of importance for this relation.

31 Stephan Neuhaus, 'OLG Düsseldorf: Zweckgebundene Stoffschutzansprüche – Östrogenblocker, m. Anm. Neuhaus' (2017) 11 GRUR 1107, 1112.

32 Bently and Sherman (n 19) 375.

33 In the UK, 83 percent of all prescriptions are written generically, cf Papadopoulou (n 21) 481.

34 Bühling (n 16) 63.

35 Schäffner (n 18) 450.

36 U Reese and C Stallberg, Handbuch des Pharmarechts (Peter Dieners and Ulrich Reese eds, 1st edn, C.H. Beck 2010), § 17 margin no 272; This is amplified by the fact that prescriptions are now created with a software, that automatically informs the physician of the substitution possibility, cf Kühne (n 26) 453.

37 Hufnagel (n 7) 124; Zigann (n 27) 249; this is also the case in other countries, such as the UK, cf Matthew Fisher, 'Second medical indications and the Swiss-from claim: taming Frankenstein's monster: Part 2 – putting the problem in context' (2017) 39 EIPR 639, 640.

38 Schäffner (n 18) 450.

39 Zigann (n 27) 249.

40 Ibid.

41 Hufnagel (n 7) 123.

42 BGH Antivirusmittel MDR 1987, 932.

43 BGH Antivirusmittel, Leitsatz a).

44 K Bacher, Patentgesetz (Georg Benkard ed, vol 4, 11th edn, C.H. Beck 2015), § 1 margin no 38b-38c.

45 Zigann (n 27) 247.

46 Art. 10 and 11 of Directive 2001/83 of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (as amended).

47 Fisher, 'Second medical indications: Part 2' (n 71) 639 ff; this is implemented into German law by § 11a(1)(1e) of the German Medicines Act (Arzneimittelgesetz).

Following the rules on manifest arrangement set out above, this is not infringing behaviour, even though the drug can be used for the patented indication due to 'cross-label' or 'off label' use.[48] Off-label use describes any case where a physician prescribes a drug for an indication that is not mentioned on the label.[49] The term cross-label use is more specific; it means the case where a drug is prescribed or handed out for an indication for which the active ingredient is generally approved, but which is not mentioned on the label.[50] The problem described above that occurs due to the social law requirement to substitute medicaments according to § 129(1) SGB V falls under cross-label use.[51] This occurrence is amplified by the fact that most prescriptions do not mention the indication for data protection reasons since the indication allows a conclusion to be drawn regarding the condition of the patient, which falls under medicinal confidentiality.[52] This means that it is impossible for the pharmacist to avoid cross-label use as they are only provided with the active ingredient and have no information as to the purpose of the intended use.

Thus, by applying a skinny label, a generic pharmaceutical company could ostensibly avoid infringing a second medical use patent as the product would not be deemed as being manifestly arranged for the patented use. Effectively though, this can be used as a method of circumventing the patent since the product will still be used for the patented indication due to the substitution obligation.[53] Therefore, the position developed by the courts on how to assess skinny labels in finding infringement plays an important role in shaping the scope of protection.

i. Ribavirin

One of the important decisions to deal with the effects of a skinny label was the 2004 *Ribavirin* decision[54] of the Regional Court of Düsseldorf (LG Düsseldorf). In the case, the patent holder brought a legal action claiming infringement of the patent for the use of ribavirin in the manufacture of a medicament for use in a combination therapy to remove HCV-RNA in patients suffering of a chronical hepatitis-C infection.[55] According to the court, the reason for which the patent was granted and the invention seen as inventive was that it claimed the efficacy of this treatment for a specific patient group that was described by three specific features.[56] The contested product that was marketed by the defendant did not mention this specific patient group on its label.[57] However, the claimant was of the opinion that the patent was infringed since the general patient group of patients infected with HCV (as mentioned on the label) comprised this specific patient group.[58] Additionally, they pointed out that of the patients infected with HCV, more than half pertained to the specific patient group mentioned in the patent claims.[59]

As mentioned above, the point of reference for all courts dealing with second medical use cases is the *Zweckbindung* of these types of claims. In this case, the LG Düsseldorf argued that the purpose laid in the treatment of the specific patient group.[60] Therefore, it did not matter that the specific patient group was included in a more general patient group. According to the court, it could also not matter that the specific group made up more than 50 % of the more general patient group, since such a protection would not be purpose-bound and thus exceed the scope of protection conferred by the patent.[61] To support their stance, they referred to the above mentioned *Antivirusmittel* decision,[62] in which the BGH stated that it could not be considered that a purpose-bound patent was carried out simply because the effects described in the patent occurred as what can be described as a side-effect.[63] Consequently, the outcome of this decision is that the content of a label, in this case a skinny label, is the main point of reference when it comes to determining if a patent was infringed. This leads to the conclusion that a skinny label is a safe harbour for patent infringement. In other words, if the patented indication is carved out on the label, there can be no infringement even if the product is actually (also) used for that indication.

ii. Chronische Hepatitis C-Behandlung

The LG Düsseldorf confirmed its decision in a 2013 ruling named *Chronische Hepatitis C-Behandlung*.[64] The case was fairly similar to the Ribavirin case in that the patent in suit in both cases related to the treatment of patients with chronic hepatitis-C and that both patents described a treatment that was particularly effective for a specific patient group defined by a number of specific features. The court reiterated its opinion that there was no manifest arrangement for the patented use even if the claimed patient group was included in the patient group mentioned on the label in suit and that this finding was not altered by the fact that the claimed patient group make up an important part of the patient group mentioned on the label.[65] As far as the significance of this confirmation goes, it should be noted that both decisions were not only made by the same court but also by the same chamber. However, the decisions are nine years apart and so the fact that the court decided in the same way and specifically confirmed its earlier decision should give the reasoning some weight.

iii. Cistus incanus I and II

The impacts of a skinny label were also addressed in *Cistus incanus I*[66] *and Cistus incanus II*,[67] two parallel decisions from 2013 by the Higher Regional Court of Düsseldorf (OLG Düsseldorf). The relevant question in both cases was whether general advertisement announcements (*allgemeine Werbeankündigungen* in the original German version) such as flyers, brochures or statements by the sales representatives that contained the patented indication could lead to a manifest arrangement of the product, even though the product itself was marketed and distributed with a skinny label carving out the patented indication. The claimant[68] argued that this was sufficient to demonstrate that the generic company, which distributed the product, aimed to do so also for the purpose of treating the patented indication.[69]

When it comes to striking a balance between the two positions mentioned at the beginning of this section, this reasoning is understandable. Even though the generic company does not include the patented indication on their label, they want to spread awareness about the fact that the product is objectively suited not only for the patent-free indication(s) mentioned on the label, but also for the one still protected by a second medical use patent. The motive for this might be that doctors or pharmacists will keep this specific generic in mind when they prescribe a product for the patented indication and not dismiss it because of the carve out. Considering the above mentioned factors regarding the social and regulatory law system in Germany, the positive effect of such actions is questionable. Nevertheless, the question remains whether these actions are to be considered as manifest arrangement or as contributing to manifestly arranging the product.

The opinion of the court was that such general advertisement announcements address the patented use in a manner, which is detached from the actual offer and sale of the product.[70] Therefore, it could not lead to the conclusion that the concerned product was manifestly arranged for the patented use. The reasoning behind this is that because these announcements are detached from the offer and sale of the product, it is uncertain if the recipient of the product even notices them.[71] Consequently, according the court, it cannot be determined whether the announcements have led to the patented use.[72] This reasoning was confirmed and supported in *Chronische Hepatitis-C Behandlung* later in the same year.[73] While the court in *Chronische Hepatitis-C Behandlung* is lower in hierarchy to the Higher Regional Court, it is still an affirming sign that the reasoning was mentioned and fully adopted by the Regional Court.

Similar to *Ribavirin*, the court followed a strict principle when deciding on manifest arrangement and thus on patent infringement. This principle can be summarised as follows: infringement can only occur if the product has been manifestly arranged for the patented use and this is the case only where there is an extremely close relationship between the arrangement and the product. Therefore, the content of a Package Leaflet (PL) is decisive for determining if the product in question has been manifestly arranged. While this principle has the advantage of providing a simple test for infringement and promoting legal certainty, it is questionable whether it takes all elements of the claim into consideration and adequately balances the positions at stake. It could be argued that the position taken by the courts favours generic companies by making it easier for them to enter the market without a significant risk of infringing a second medical use patent.

With regard to the scope of protection of Swiss-type claims, the position adopted by the courts in the reviewed decisions is that the scope is strictly limited by requiring any infringing use to be purpose bound. Throughout all decisions, the courts do not cease to repeat the importance of this limitation. The courts try to adhere to this purpose requirement by demanding an especially narrow relationship between the (contested) manifest arrangement and the offer/sale of the product. Hence, it can be concluded that (until 2013), the German courts took the position of a narrow scope of protection for second medical use claims in their infringement decisions.

48 Hufnagel (n 7) 124.
49 More specifically, it describes any prescription of the drug that is contrary to its approved MA, purpose, patient group, or indication; Isabelle Vrancken, 'Off-label Prescription of Medication' (2015) 22 EJHL 165.
50 Hufnagel (n 7) 123.
51 Jürgen Dressel in 'Roundtable: The Second Medical Use Challenge' (2017) 265 Managing IP 26, 27.
52 von Falck and Gundt (n 6) 117; Schäffner (n 18) 450.
53 Schäffner (n 18) 451.
54 LG Düsseldorf Ribavirin GRUR-RR 2004, 193.
55 Ibid [2].
56 Ibid [52].
57 Ibid [10].
58 Ibid.
59 Ibid.
60 Ibid [52].
61 Ibid [56].
62 Ibid [77] ff.
63 In the specific case, a pharmaceutical medicament "X" was administered for the treatment of Parkinson's disease. Occasionally, this also had the effect of a prevention against viral diseases, ie the patented indication.
64 LG Düsseldorf Chronische Hepatitis-C Behandlung D-Prax Nr. 2011.
65 Ibid Reasons II. 3. b).
66 OLG Düsseldorf Cistus incanus I BeckRS 2013, 03824.
67 OLG Düsseldorf Cistus incanus II BeckRS 2013, 11782.
68 For the purpose of facilitating the account of the cases and focusing on the relevant issues, the patent holder is referred to as claimant, which corresponds to the situation in Cistus incanus I. In Cistus incanus II, the generic company sued the patent holder for refund of, inter alia, legal fees, so that in this particular case the patent holder is in fact not the claimant but the defendant.
69 OLG Düsseldorf Cistus incanus I [21]; OLG Düsseldorf Cistus incanus II [33].
70 Ibid I [87]; II [139].
71 Ibid.
72 Ibid.
73 LG Düsseldorf Chronische Hepatitis-C Behandlung, Reasons II. 2.

3.1.3. Introducing limitations to the 'Safe Harbour' – The Pregabalin cases

In 2015, this position was questioned by five parallel decisions in preliminary injunction proceedings[74] from the Regional Court of Hamburg (LG Hamburg) called *Pregabalin*. They all concerned the infringement of Warner-Lambert's aforementioned patent whose corresponding product is marketed under the brand name of Lyrica® by various generic pharmaceutical companies.[75] The substance pregabalin has a number of different indications out of which one – namely the treatment of neuropathic pain – was still protected by a patent.[76] The others, inter *alia* epilepsy and generalised anxiety disorder, are patent free.

The facts of the case can be summarised as follows: the defendant, a generic company, markets and distributes a generic product with the substance pregabalin. To do so, they use a so-called skinny label, which only contains the patent free indications.[77] To distribute their product, the defendant has entered a rebate agreement with a health insurance company, whereby the rebate agreement concerns the substance pregabalin without any restrictions with regard to the patented indication.[78]

The court granted a preliminary injunction against the defendant, prohibiting them to enter into such an unrestricted rebate agreement. When it came to their reasoning, the court laid the foundation for the decision by clarifying that skinny labelling did not impede the possibility of indirect patent infringement because in this case the infringement was a foreseeable consequence of entering into an unrestricted rebate agreement.[79] After that, the court elaborated on the topic of manifest arrangement. In this regard they started by mentioning that it was questionable whether manifest arrangement was necessary for indirect infringement.[80] Leaving this question unanswered they stated that, in this case, the product was manifestly arranged through its production,as its mere existence was sufficient for a manifest arrangement in this case.[81] This is because the preparation is an essential means of the invention and the only missing factor for a direct patent infringement is the use for the indication 'neuropathic pain', which is added by the pharmacist handing out the product.[82] This, in turn, is certainly foreseeable because of the social obligations that follow from §§ 129, 130 SGB V.[83]

By assuming that the production of the product was sufficient for its manifest arrangement, the court explicitly contradicted the LG Düsseldorf in *Ribavirin*, which had then stated that a patent could only be indirectly infringed by offering and/or selling the product, if this occurred to allow a manifest arrangement of the product (in a second step) and not for its direct administration.[84] Hence, the offer and/or sale of the product itself could not constitute a relevant act for indirect infringement. However, it has to be kept in mind that the reasoning in *Pregabalin* is mainly based on the fact that a patent infringement was fairly obvious due to the implicated social law regulations. Insofar, the two cases are different and cannot be compared directly.

The OLG Düsseldorf had to decide on a different aspect of the same issue.[85] They faced the question of whether the health insurance company could rightfully start tender proceedings for an unrestricted rebate agreement for the substance pregabalin in the sense that it did not take out the patented indication for neuropathic pain. They concluded that because of how the tender was formulated it was likely that the product would be used in the patented way, that is for the treatment of neuropathic pain.[86] Therefore, the court suggested that the most secure solution in these types of cases would be to have separate tenders for the patented indication of pregabalin on the one side and for the other patent-free indications on the other side.[87] This decision shows that when it comes to unrestricted rebate agreements, the position of the courts is quite clear: an unrestricted rebate agreement will undoubtedly lead to patent infringement, which cannot be tolerated since it is evitable. It is not only unlawful to enter such a rebate agreement, but also to start tender proceedings for this type of agreement. While social law and patent law will continue to collide on this issue, where patent law can easily be enforced without disregarding the legal consequences that social law regulations bring with them, this should be done.[88]

By re-evaluating the relevant issues and introducing limits to this 'safe harbour' that had been the skinny label, the decision in *Pregabalin* is highly relevant not only for the industry, but also in its significance for the scope of protection conferred by Swiss-type claims. It opens up the possibility to include more actual circumstances when finding infringement or manifest arrangement and in doing so tries to strike a better balance between the concerned rights.[89] This patent owner friendly attitude is in line with further current European decisions on the topic that seem to be in favour of a wider scope of protection for Swiss-type claims.[90] While it would be interesting to see whether the courts of higher instance confirm this decision, such a decision is precluded as the patent in suit was annulled in 2017 and thus, the motion in the second instance was withdrawn.[91]

3.1.4. Putting an end to the 'manifest arrangement' requirement – Östrogenblocker

Most recent developments in case law seem to confirm this attitude. A landmark decision in this regard is the *Östrogenblocker* ruling of 2017 by the OLG Düsseldorf,[92] which suggests that the German jurisprudence is moving away from the strict requirement of manifest arrangement that it has applied for years.

In the specific case, the court dismissed the case on the grounds of non-urgency.[93] However, what is relevant about this decision is that it provides clear guidance on both the relationship between Swiss-type and EPC 2000 claims and the consequences for infringement cases.

The court does this by elaborating on purpose-bound product protection. It reasons that the latter is always conferred when the patented use of the protected product is actually guaranteed, irrespective of whether the person liable for this (through manifest arrangement) is the one offering the product.[94] In other words, it comes down to a *de facto* patented use of the product and not to the behaviour of a supplier. This goes back to the particularities of purpose-bound protection. These entail that the acts mentioned in § 9 Patentgesetz, the section governing direct patent infringement, must occur with the goal to lead to a specific objective (the purpose).[95] This is in line with what was mentioned at the very beginning of this section and is another example of how *Zweckbindung* is the leading principle when it comes to assessing infringement of purpose-bound claims. According to the court, in order to find direct patent infringement, the patented purpose has to be immanent in the product offered or distributed.[96] This can be done either by manifest arrangement or otherwise, since the relevant factor is that the pharmaceutical is objectively suited for the patented use.[97] The court argues that – provided that the product is objectively suited for the patented use – it would not be appropriate to refuse patent protection in cases where the patented use occurs due to other circumstances than the manifest arrangement, for instance in cases of cross-label use.[98] To avoid any confusion, the court then provides a set of prerequisites to ensure the existence of *Zweckbindung*,[99] meaning that the product in suit is in fact intended for a specific purpose (otherwise put purpose-bound), which can be structured as follows:

1) The product has to be suited for the patented use.
2) The distributor has to take advantage of circumstances that ensure that the pharmaceutical is used for the purpose-bound therapeutic use, similarly to a manifest arrangement. This requires the following:

   a) The patented use needs to occur on a sufficient scale; isolated or occasional occurrence is not sufficient.
   b) The distributor needs to have knowledge thereof.[100]

To come back to consequences for infringement cases, the most important ramification is surely that by considering other factors aside from manifest arrangement, infringement is conceivable despite the use of a skinny label.[101] This is because the court has distanced itself from the requirement of manifest arrangement that had been applied strictly for years and had greatly influenced the jurisprudence in Germany in the field of infringement of second medical use claims. In doing so, the court is in line with demands in the relevant literature, which spoke out in favour of focusing on whether the product was objectively being used in the patented way instead of insisting on manifest arrangement.[102] The system set up by the OLG Düsseldorf in *Östrogenblocker* provides a new way of finding infringement in second medical use cases, which is still clear and can be applied objectively. Its clarity is what makes the manifest arrangement-requirement especially appealing and successful, hence it seems important that the new requirement be similarly unambiguous. Another advantage of this approach is that it provides a solution in which an appropriate balance can be achieved between the interests of originator companies in their role as patent holders on the one hand and generic companies as well as the general public, which benefit from the use of non-patented and thus cheaper pharmaceuticals, on the other hand.[103] Ultimately however, this development strengthens the protection of second medical use patents,[104] which are highly important for innovator pharmaceutical companies.[105]. At the time of submission of this article, the LG Düsseldorf has published three parallel decisions that apply the requisites set out in *Östrogenblocker*.[106] It will be interesting to see whether other courts, especially courts of the Highest Instance, will follow suit.

Another highly significant finding of this decision is that it confirms the position taken by the BGH in *Pemetrexed*,[107] according to which Swiss-type and EPC 2000 claims do not differ from one another with regards to their scope of protection but rather both provide purpose-bound product protection.[108] This is in contrast to earlier opinions, which assumed that the Swiss-type claims confer purpose-bound use protection. As the Pemetrexed decision came from the court of highest instance, the BGH, it was given weight. This is intensified by the fact that the OLG Düsseldorf so unambiguously adopted it.

74 LG Hamburg Pregabalin, docket numbers 315 O 24/15; 327 O 67/15; 327 O 143/15; 327 O 132/15; 327 O 140/15, published as GRUR-RR 2015, 330.
75 The defendant generic companies distributing pregabalin were Ratiopharm, Hexal, 1A Pharma, Glenmark, and Aliud Pharma.
76 Filing date: 16 July 1997, LG Hamburg Pregabalin [5], [10].
77 LG Hamburg Pregabalin [17].
78 Ibid [18].
79 Ibid [88].
80 Ibid [90].
81 Ibid [92].
82 Ibid.
83 Ibid.
84 LG Düsseldorf Ribavirin, Leitsatz 2.
85 OLG Düsseldorf BeckRS 2016, 02948.
86 Ibid [23].
87 Ibid [28].
88 Having separate tenders according to the indication is described as a possible practice in competition law, but it is noted that it entails a greater challenge for the contracter and thus this practice would require special justification, cf M Gabriel, Münchener Kommentar Europäisches und Deutsches Wettbewerbsrecht (Franz Jürgen Säcker ed, vol 3, 2nd edn, C.H. Beck 2018), 4. Teil, margin no 78.
89 The same conclusion was reached in Schäffner (n 18) 450; 455.
90 Zigann (n 27) 245 with references to the specific decisions.
91 Schäffner (n 18) 450.
92 OLG Düsseldorf Östrogenblocker GRUR 2017, 1107.
93 Ibid [56].
94 Ibid [70].
95 Ibid [72].
96 Ibid.
97 Ibid [73].
98 Ibid.
99 Ibid.
100 Ibid [73].
101 Stephan Neuhaus, 'Patentverletzung von "Second Medical Use"-Ansprüchen durch Produkte mit sog. "Skinny Label" – OLG Düsseldorf, Beschl. v. 5.5.2017, I-2 W 6/17 – Östrogenblocker' IPunkt January 2018, 8, ←https://f.datasrvr.com/fr1/018/67701/Patentrecht_Neuhaus_Second_Medical_Use.pdf→ accessed 23 April 2018; Schäffner (n 18) 452.
102 von Falck and Gundt (n 6) 124.
103 Neuhaus (n 31) 1112.
104 Schäffner (n 18) 452.
105 Neuhaus in IPunkt January 2018 (n 101).
106 LG Düsseldorf, docket numbers 4c O 46/17; 4c O 47/17; 4c O 10/18, all dated 5 July 2018.
107 BGH Pemetrexed GRUR 2016, 921.
108 Ibid [83] ff.

3.2. Infringement of EPC 2000 claims

It can be expected that infringement cases in which EPC 2000 claims are concerned will surface in the next years and it remains to be seen how the jurisprudence will react to these. However, the decision in Pemetrexed, as confirmed by the decision in Östrogenblocker, can be interpreted as a sign that the courts are preparing themselves for these cases. By clarifying that both claim types shall be treated equally with regard to their scope of protection, meaning that the protection conferred by Swiss-type claims shall be the same as the one conferred by EPC 2000 claims, the courts have laid the foundation for future cases. They can now continue to develop their jurisprudence, irrespective of the claim formulation with which they are faced. This way, they do not need to develop different jurisprudence and argumentation lines for both claim types respectively, but can simply treat them as second medical use claims providing purpose-bound product protection. While neither Pemetrexed nor Östrogenblocker mention that this reasoning has anything to do with the fact that the courts will shortly be finding infringement of EPC 2000 claims, it is a valid assumption. Of course, the rise of infringement cases concerning EPC 2000 claims would only be one of many reasons for this consequential decision, which is much in line with the general development of the jurisprudence in the field of second medical use claims.

3.3. Significance for the scope of protection of second medical use claims

After considering all the different factors that come into play when finding infringement of second medical use cases, it can be concluded that the national case law plays a great part in defining the scope of protection of second medical use claims. Since national courts are faced with the actual effects of a scope of protection that is either narrower or wider, this allows them to have a more practical view on what type of scope actually makes sense for the enforcement of a claim type. An important consequence of the (current) European patent law system in which only the pre-grant phase is harmonised is that the EPO will never be confronted with patent enforcement cases, which seemingly makes it harder for them to consider the downstream effects of their decisions. While this is comprehensible, it is also the root of many problems.

In the EPO case law regarding the possible differences between Swiss-type and EPC 2000 claims with regard to their scope of protection, the main and recurring argument was the difference in claim category. When solely considering the claim category, the only logical solution seemed to be that EPC 2000 claims confer a broader scope of protection, since they are purpose-bound product claims, whereas Swiss-type claims are purpose-bound process claims.

The national courts, such as the BGH in Pemetrexed, have the advantage of years of experience in dealing with the enforcement of second medical use patents and developing a jurisprudence that would allow a reasonable balance between the above mentioned rights. This explains why their focus is more on the actual effect of a claim rather than on a claim category. In Pemetrexed, the BGH tried to identify the actual subject-matter protected by a Swiss-type claim and came to the conclusion that in fact, this corresponds to a purpose-bound product protection, hence, the protection conferred by EPC 2000 claims. Therefore, the scope of protection conferred by both claim types is equal, irrespective of their formulation. This finding is very much in line with the outcome of the conducted study of the preparatory works, which demonstrates that the main aim behind the EPC 2000 claims was to codify the (then) current jurisprudence regarding Swiss-type claims. Swiss-type claims had only taken the form of process claims because they required a formulation that can only be described as a work-around. Thus, it can only be seen as positive that the BGH focused on the actual subject-matter of both claim types instead of being blinded by their different formulations and the claim categories these entail.

The complexity of the factors to be considered also explains why the jurisprudence has developed as much as it did: the courts are constantly trying to adjust the balance in order to do justice to all relevant rights. The recent developments in the German case law provide a welcome solution to the longstanding debate on the scope of protection of Swiss-type and EPC 2000 claims. It seems that the courts have strengthened the legal status of second medical use patents and achieved a reasonable balance between the rights involved. Additionally, they show a welcome movement away from the dogmatic requirements of manifest arrangement towards a new approach, which includes more relevant factors and so allows for more adequate solutions when finding infringement. This perception is shared by the most recent specialised literature.[109] Finally, the courts lay the ideal foundation for futurecases in which the national courts will be faced with finding infringement of EPC 2000 claims.

4. FINDINGS AND CONCLUDING THOUGHTS

As demonstrated by this article, second medical use claims - irrespective of their formulation - are highly complex and require the consideration of many aspects which go back to the core of patent law. Trying to enforce second medical use claims demands a careful balancing of the rights at stake such as the right of the patent holder to a fair protection of the second medical use patent on the one hand, and the right of third companies to make use of the patent-free first indications on the other, which in turn goes hand in hand with the right of the general public to access cheaper, generic pharmaceuticals after the patent has run out. Additionally, the situation is made even more complicated by the interference of social and regulatory law, since a balance between these two regulations needs to be achieved as well.

In the EPC 1973, second medical indication inventions - unlike inventions for the first medical indication - were not considered to be patentable. After the general need for patenting these kinds of inventions was recognised, the latter could first be patented in the form of Swiss-type claims in the EPO's landmark decision in 1984. Later, second medical use claims were introduced into the EPC as part of the reformations that resulted in the EPC 2000.

The EPC 2000 claims were supposed to codify the common jurisprudence regarding Swiss-type claims especially with regard to their scope of protection. However, the new formulation resulted in a different claim category. Thus, the scope of protection conferred by EPC 2000 claims as purpose-bound product claims was de facto broader than the one conferred by Swiss-type claims, which are purpose-bound process claims. This was confirmed by a number of EPO judgements, both from the EBA and the Boards of Appeal. This was in contrast to the intention of the drafters of the EPC, as shown in the travaux préparatoires for the revision of the EPC. In Germany, the BGH in Pemetrexed remedied this divergence between the intention of the drafters of the EPC and the actual legal situation by focusing on the actual subject-matter of the two claim types. Consequently, the BGH came to the conclusion both claim types confer purpose-bound product protection.

After having established the scope of protection of both Swiss-type and EPC 2000 claims from the position of the EPO, it is also important to consider the significance of national patent enforcement jurisprudence. On the one hand, the scope of protection conferred by a claim is highly relevant for finding infringement, since infringement can logically only occur where there is patent protection. This means that the courts are somewhat bound by the scope of protection of a claim. On the other hand, where the scope of protection is not inherently clear, it is in the hands of the court to carefully assess which acts constitute infringement. In doing so, the national courts contribute to shaping the scope of protection.

Especially in the last decade, the German national courts have dealt with numerous infringement cases involving second medical use claims and have faced the challenge of striking a balance between the aforementioned rights. The case law assessed in Section 3 shows the complexity of this task. This is amplified by the fact that the enforcement of patent law collides with regulatory guidelines from social law that need to be respected. Namely, the substitutive obligation for pharmacists pursuant to § 129(1) SGB V, rebate agreements pursuant to entered between generic companies and health insurance companies pursuant to § 130a(8) SGB V. Added to this, it is the pressure that physicians face to prescribe generically rather than by reference to the patented products. Collectively, these factors promote cross-label use of pharmaceuticals, which makes it difficult to identify infringement. As demonstrated by this study, until 2013 it seemed that the German courts considered a skinny label to provide a 'safe harbour' from infringing second medical use patents. By focusing solely on the German requirement of manifest arrangement, they concluded that a generic product with a skinny label, meaning that the patented indication had been carved out from both the SmPC and the PL, had not been manifestly arranged for the patented use. Thus, any actual use of the product for the patented use related to cross-label use could not be attributed to the generic company.

In recent court decisions, the courts have instead moved away from the strict dogma of manifest arrangement and involved additional aspects in finding infringement of second medical use claims. The focus now lies on determining if the patented use actually occurs on a greater scale and whether the generic company somehow intended this. As seen in this article, this is a welcome change of direction, which also finds support in the relevant specialised literature. It seems that the criteria established by the newest developments in jurisprudence allow a balance between the above mentioned rights. Additionally, by implementing the jurisprudence of the BGH in Pemetrexed concerning the scope of protection of both types of second medical use claims, which were deemed to confer purpose-bound product protection, the courts have laid the basis for future cases involving EPC 2000 claims.

In the future, it will be interesting to observe how the courts further develop their jurisprudence and, in doing so, shape the scope of protection of second medical use claims. It will be of particular interest to see, firstly, how the national courts address cases involving EPC 2000 claims and, secondly, what stance the Unified Patent Court will take on this matter.

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[74] cf Neuhaus (n 31), but also more recently Schäffner (n 18) and Kühne (n 26) in the May 2018 issue of GRUR.

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Do rules experience culture shock?

– Interpreting Article 3(a) of the Supplementary Protection Certificate Regulation: is the donor rule faulty or is the transplanted rule incompatible with its new legal environment?

By Lisa West Åkerblom

TERMINOLOGY IN THIS ARTICLE

"Patent term extension" is used generically to refer to an additional time of protection in relation to a pharmaceutical product which is the subject of protection by a patent. "Patent term restoration" is the term used when referencing the U.S. extension, while the "Supplementary Protection Certificate", or SPC, refers specifically to the EU instrument.

ABSTRACT

In order to stimulate product development and innovation in the pharmaceutical industry, the United States Congress in 1984 enacted Title II of the Drug Price Competition and Patent Term Restoration Act (Public Law 98-417), also known as the Hatch-Waxman Act. One goal of the Hatch-Waxman Act was to extend patent life to compensate patent holders for a portion of the patent term lost while awaiting review of the safety and efficacy of the product by the Federal Drug Administration.

Influenced by the United States, the European Union (EU) introduced legislation in 1992 offering the possibility for a patent holder to apply for an additional time of protection as compensation for the regulatory delays caused by marketing authorization procedures. This additional time period of protection is granted in the form of a Supplementary Protection Certificate (SPC), governed by an EU Regulation.[1]

As the subject matter protected by the SPC, the product is defined as "the active ingredient or combination of active ingredients of a medicinal product."[2] The term product within the context of the SPC Regulation is an independent term which cannot be equated with the patented invention or marketing authorization.[3] The product for which the SPC is sought must be protected by a basic patent in force,[4] which is also a condition for patent term extension in the United States.[5]

The interpretation of product and its relation to the patent in force is a central condition to determine if a certificate may be granted.[6] There has been divergence in the application of this condition by the national courts and a stream of requests for preliminary rulings. Legal uncertainty in interpretation remains due to the lack of clear guidance from the Court of Justice of the European Union (hereinafter "CJEU").

This article examines the material condition of the SPC Regulation requiring that a product be protected by a basic patent, from its origin in the United States to the legislation and institutions of the European Union, in order to investigate rules as an institutional phenomenon. Do the issues of interpretation with Article 3(a) of the SPC Regulation arise at the fault of the borrowed material legal solution itself, or do they occur from transplanting the solution from its native environment into a new legal system? The answer as the reader will discover is both.

1.0 INTRODUCTION

The process of bringing a medicinal product to market is time-consuming, expensive and subject to failure. The testing and regulatory process to receive approval to market medicinal products erodes the time a product has exclusive rights under the protection of a patent. In some cases, patents expire even before a medicinal product is approved to be placed on the market. Upon the expiration of a patent, sales of the formerly patented product drop significantly as instant competition opens up to its generic version by competitors, generating a loss of revenue for the firm whom once held the patent.[8]

The pharmaceutical sector performs a crucial role in our society through their research and production of new medicinal products.[9] The interest of society rests in between the competing interest of the large pharmaceutical firms (to ensure the on-going development of new medicinal products) and the generic manufacturers (to bring down the cost). The generic manufacturers of pharmaceutical drugs have an interest themselves in patents being pursued by and granted to large pharmaceutical firms so the "know-how" behind the new product is disclosed, allowing for eventual generic reproduction.[10] Government holds an interest in ensuring that expenditure in the public health sector is not artificially increased due to patent term extension of products containing old active ingredients which are simply modified without innovation and marketed as a new product.[11]

Adequate regulatory measures are required to balance all interests at stake in this complex environment and to promote an innovation culture. Patent term extension can encourage the development of new drugs through the incentives it provides to patent owners, addressing the decline in the rate of return to R&D investments attributed to the reduction in the effective patent term.[12]

To stimulate product development and innovation, the United States (U.S.) Congress in 1984 enacted Title II of the Drug Price Competition and Patent Term Restoration Act (Public Law 98-417), also known as the Hatch-Waxman Act. The goal of the Act was to extend patent life to compensate patent holders for a portion of the patent term that is lost while the patent holder is awaiting regulatory review of the safety and efficacy of the product. The restoration period cannot exceed five years and the total patent term including the restoration period cannot exceed 14 years following marketing approval.

In 1990 the European Commission expressed concern over a drop in the number of "molecules of European origin that have reached the research and development stage" and the "(...) slow erosion of the European market shares as compared with those of the USA and Japan(...)" who "(...) since 1984 and 1988 respectively, benefitted from patent term restoration for pharmaceutical products on their national markets."[13]

The European Supplementary Protection Certificate (SPC) Regulation[14] was first established in 1992,[15] introducing a European Union (EU) legal instrument of patent term extension borrowed from a foreign legal system in order to provide EU law reformers an efficient solution to an identified problem.

An SPC comes into force only after the corresponding patent expires and relates to a specific product. It has a maximum lifetime of five years and the total combined duration of market exclusivity of a patent and SPC cannot exceed 15 years.[16]

Certain criteria must be fulfilled prior to the successful grant of a patent term extension. The commercial importance of the products that it protects has meant that the SPC regime is challenged by conflicting interests. A pivotal issue in the grant of an SPC is the interpretation of Article 3(a) of the SPC Regulation which, similarly to the award of a period of patent term restoration in the U.S., requires a basic patent in force protecting the *product* in question.[17]

This article will draw conclusions to which extent the jurisprudence of the transplanted rule has undergone transformation due to the difference in law-making institutional structure in its new environment.

2.0 U.S. DONOR LEGISLATION AND ITS INSTITUTIONAL ENVIRONMENT

2.1 U.S. Patents

United States (U.S.) patent law is codified in Title 35 of the United States Code (35 U.S.C.) and authorized by the United States Constitution which declares: "The Congress shall have power...To promote the progress of science and useful arts, by securing for limited time to authors and inventors the exclusive right to their respective writing and discoveries."[18]

Under U.S. law, a patent is a right granted to an inventor of a process, machine, article of manufacture, or composition of matter that is new, useful and non-obvious.[19] A patent is an intellectual property right to exclude others from making, using, selling, offering for sale, importing, inducing others to infringe, and/or offering a product specially adapted for practice of the patent.[20] After the patent term expires, the invention, along with the know-how contained within the patent filing, enters the public domain and competition ensues.

2.2 U.S. Patent Term Restoration

In 1978, U.S. President Jimmy Carter called for a domestic policy review of industrial innovation. One outcome of the policy review was a recommendation by two sub-committees to lengthen the term of pharmaceutical patents to compensate for the time consumed in meeting government regulatory requirements.[21] President Reagan's Cabinet Council on Commerce and Trade supported the proposal and set up an intellectual property committee. The committee recommended, and the Cabinet Council supported, the introduction of patent term restoration.[22]

1 Regulation (EC) No 469/2009 of the European Parliament and of the Council of 6 May 2009 concerning the supplementary protection certificate for medicinal products (hereinafter "SPC Regulation").
2 SPC Regulation, article 1(b).
3 The German Association for the Protection of Intellectual Property, Journal of Intellectual Property Law & Practice, 2013, vol 8, no. 9, p. 723, citing German Federal Court of Justice (BGH), GRUR 2002, p. 415 Sumatriptan.
4 SPC Regulation, article 3(a).
5 Title 35 United States Code §156(a)(1).
6 SPC Regulation, article 3(a).
7 Adams, John N., "Supplementary Protection Certificates: The challenge to EC Regulation 1768/92", European Patent Convention Article 83 (1994) EIPR 16(8), p. 323.
8 Opinion of Advocate General Trstenjak delivered 13 July 2011 on C-322/10 Medeva BV and C-422/10 Georgetown University v Comptroller General of Patents, Design and Trademark, ECLI:EU:C:2011:476, para 77. (Hereinafter AG Opinion Medeva).
9 SPC Regulation, articles 2-3.
10 Commission of the European Communities, "Proposal for a Council Regulation (EEC) concerning the creation of a supplementary protection certificate for medicinal products" COM (90) 101 final – SYN 255 (April 1990), p 14. (Hereinafter "Explanatory memorandum").
11 AG Opinion on Medeva, supra n 8, para 77.
12 Patent-Term Extension and the Pharmaceutical Industry, August 1981, NTIS #PB82-100918.
13 Explanatory Memorandum supra n 10, § 6.
14 SPC Regulation, supra n 9.
15 Council Regulation (EEC) No 1768/92 concerning the creation of a supplementary protection certificate for medicinal products.
16 The maximum time of 15 years is not including any possible paediatric extension.
17 SPC Regulation, supra n 9, article 3(a) and Title 35 United States Code § 156(a)(1).
18 United States Constitution, Article One, section 8, clause 8.
19 Title 35 of the United States Code §§ 101-103.
20 Title 35 of the United States Code § 154(a)(2).
21 See Advisory Committee on Industrial Innovation, Final Report, iii at 70 (recommendation no 8 of the Health and Safety Industrial Subcommittee) and at 157 (proposal VI of the Industrial Subcommittee for Patent & Information Policy).
22 Mossinghoff, G., Overview of the Hatch-Waxman Act and Its Impact on the Drug Development Process, Food and Drug Law Journal, 1999, volume 54, p. 188.

In 1984, the U.S. Congress enacted the Drug Price Competition and Patent Term Restoration Act, commonly known as the Hatch-Waxman Act, which amended the Federal Food, Drug and Cosmetic Act[23] and the Patent Act.[24] The goal was to strike a balance between incentivizing brand pharmaceutical companies to invest in research and encouraging generic entry to reduce market prices.

The patent restoration provisions are just one part of the intricate and complex compromise embodied in the Hatch-Waxman Act of 1984 intended to positively impact the pharmaceutical business in the United States.[25] It is worth noting that an earlier Act addressing solely patent term restoration was defeated in 1982, partly through the efforts of Representative Henry Waxman of California who made clear that any future legislation would have to deal with his concerns relating to the approval of generic drugs.

The Hatch-Waxman Act[26] was a major revision to U.S. law governing the regulation of pharmaceuticals. It provided a mechanism for approving generic drugs without the need to duplicate the expensive safety and efficacy studies required of the originally approved brand medicinal product. The Hatch-Waxman Act also provided several protections for the innovator companies, including several non-patent data exclusivities that limit, for specific periods of time, the ability to file an application for approval of a generic equivalent or to obtain final approval of the generic application. A particular benefit to the brand pharmaceutical companies in the Hatch-Waxman Act is the ability, under specific circumstances, to obtain restoration for part of the term of a patent that claims a new drug.[27]

The types of products permitted to receive an extension are restricted to those drug products subjected to a regulatory review period.[28] The legislation works to prevent any one patent holder from obtaining an extension on multiple patents related to the same product as only the earliest issued patent is eligible for an extension.[29]

The contents of the application for patent term restoration are laid out in detail in the U.S. Patent and Trademark Office (PTO) Guidelines.[30] To qualify for patent extension, there are five conditions which must be satisfied. First, the applicant must show that the patent for the product has not expired. Second, the application must establish that the patent has not previously been extended under the Hatch-Waxman Act.[31] Third, the applicant must establish that the product was subject to a regulatory review period prior to its marketing approval. Fourth, the applicant must show the product either represents the first permitted marketing of the product or, in the case of a process patent, the first permitted marketing of the product manufactured under the process claimed in the patent. Finally, the applicant must submit a complete application for patent term restoration to the PTO within 60 days of marketing approval by the Federal Drug Administration (FDA).[32]

Based on the information submitted, the Secretary of Health and Human Services determines the length of the regulatory review period, and the Commissioner of Patents then decides whether the patent is eligible for extension and what length of time is granted. A Certificate of Extension, which becomes a part of the Letters Patent, is then issued by the PTO.[33] The restoration period cannot exceed five years and the total patent term including the restoration period cannot exceed 14 years following marketing approval.

The FDA is responsible to assist the PTO in determining the eligibility of a product for patent term restoration and provides information regarding the regulatory review period of such product. The FDA also has the responsibility for due diligence petitions and hearings, for which the PTO is responsible for determining the period of patent extension. The FDA defers to the PTO on all matters involving the construction and validity of patent claims. The scope of rights extended are limited – for a patented product, the rights are limited to any use approved for the product.[34]

The patent term restoration provisions are codified in Title 35 of the United States Code §156 (35 U.S.C. § 156). The U.S. PTO has promulgated rules in Title 37 of the Code of Federal Regulations in sections 1.710 to 1.791 (37 CFR 1.710-1.791), and the FDA has promulgated rules in Title 21 of the Code of Federal Regulations in sections 60.1 to 60.49 (21 CFR 60.1-60.46).[35]

3. EU RECIPIENT LEGISLATION AND ITS INSTITUTIONAL ENVIRONMENT

3.1 European Patents

A European patent is a form of national intellectual property granted by a national patent authority conferring exclusive rights on a patentee.[36] Article 33 of the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS Agreement) of 1994 states that the term of protection available for patents shall not end before the expiration of a period of twenty years counted from the date of filing. Article 28 of TRIPS describes the right a patent confers upon its owner: the exclusive rights to prevent third parties from making, using, offering for sale, selling, or importing.

The EPC, amended in 2000, regulates the legal framework for granting a patent; however, it is not a European Union instrument.[37] The EPC established the European Patent Organization, which carries the task of granting European patents, and is made up of the European Patent Office (hereinafter "EPO") and an Administrative Council.[38]

Under the EPC, a European patent can be granted for any invention in all fields of technology provided it is susceptible to industrial application, novel and involves an inventive step.[39] The invention must also be disclosed in a sufficiently clear and complete manner.[40] Article 69 of the EPC stipulates that the extent of protection conferred by a patent is to be determined by its claims.

The EPC simplifies the process of filing for patents, however, it does not create a centralized European judiciary. A grant does not result in a unified European patent as its name would suggest, but instead provides for an independent patent under the national jurisdiction of the member state(s) in which an application is sought.[41] Article 64 of the EPC provides that the rights of the basic patent are those prescribed by the national state and its domestic law, under which the patent was granted.

It is worth noting that although both U.S. and EU patent term extensions require a "basic patent in force," the patents themselves are of different nature – a U.S. patent is enforceable throughout the entire U.S. territory, while an EU patent is only valid in the specific countries for which the applicant applied for protection.

3.2 EU Supplementary Protection Certificate

Similarly to the patent term extensions available in the U.S., EU law offers since 1992 the possibility to compensate European patent holders for the regulatory delays caused by marketing authorization procedures.

In 1988, the European Federation of the Pharmaceutical Industry Associations published a "Memorandum on the necessity to restore the effective duration of patents for pharmaceutical products." Shortly thereafter, the European Commission expressed concern over a "fall in the number of molecules of European origin that have reached the research and development stage" and the "(...) slow erosion of the European market shares as compared with those of the USA and Japan"who "(...)since 1984 and 1988 respectively, benefitted from patent term restoration for pharmaceutical products on their national markets."[42]

Thus, the proposal for a European patent term extension in the form of the Supplementary Protection Certificate (hereinafter "SPC"), was to "close some of the gap which has arisen between Europe and its major competitors in the international market – specifically in the USA, with the Hatch-Waxman Act."[43] In 1991, France introduced the Certificate of Complementary Protection (hereinafter "CCP") as a new intellectual property right, followed closely by a proposal for similar legislation in Italy. The Commission understood the need to create a unified solution in the community in order to support the free movement of pharmaceutical goods.[44]

The European SPC system was established in 1992 with the introduction of EC Regulation 1768/92[45] which following subsequent amendments was consolidated into Regulation 469/2009 (SPC Regulation) binding all member states of the EU.[46]

The aim of the SPC Regulation is to improve innovation in the pharmaceutical sector by providing favorable rules to ensure protection and encourage research.[47] The objectives behind the SPC Regulation outlined in the Explanatory Memorandum of the Regulation are: to provide favorable rules for sufficient protection encouraging research for medicinal products;[48] to create a uniform solution at the Community level to prevent disparities likely to create obstacles to the free movement of medicinal products;[49] to grant "adequate" protection;[50] and to take into account all the interests at stake, including the public health sector and the pharmaceutical sector.[51]

23 FDCA Pub. L. No. 75-717, chapter 675, 52 Stat. 1040 (June 25, 1983) codified as amended at 21 United States Code §§ 301-399 (2002); at 21 United States Code § 355 (2006).

24 Title 35 of the United States Code §§ 156 and 271 (2006).

25 Goldstein, Steven J., The Drug Price Competition and Patent Term Restoration Act of 1984 Title II – Patent Extension Provisions, Food Drug Cosmetic Law Journal, 1985, volume 40, p 367.

26 Public Law No. 98-417, 98 Stat. 1585 (1984), codified in 21 USC 355, 360cc (2000), 35 USC 156, 271, 282 (2000), as amended by the Medicare Prescription Drug, Improvement and Modernization Act of 2003, Public Law No. 108-173, 117 Stat. 2066 (2003).

27 Boone, Jeffrey S., Patent term extensions for human drugs under the U.S. Hatch-Waxman Act, Journal of Intellectual Property Law & Practice, 2009, volume 4, no 9.

28 Title 35 of the United States Code § 156(g).

29 Ibid, § 156(c)(4).

30 Guidelines for Extension of Patent Term Under 35 USC 156, U.S. Patent and Trademark Office Official Gazette (1984), 1047 O.G. 17.

31 Patent term adjustments under 35 USC 154(b) dealing with delays in the PTO do not limit the availability of patent term restoration under the Hatch-Waxman Act.

32 Title 35 of the United States Code 156(a)(3) and 156(d)(1).

33 Goldstein, Steven J., The Drug Price Competition and Patent Term Restoration Act of 1984 Title II – Patent Extension Provisions, Food Drug Cosmetic Law Journal, 1985, volume 40, p 366.

34 Title 35 United States Code § 156(b).

35 Boone, Jeffrey S., Patent term extensions for human drugs under the U.S. Hatch-Waxman Act, Journal of Intellectual Property Law & Practice, 2009, volume 4, no 9.

36 The Convention of the Grant of European Patents of 5 October 1973 (as amended), article 63(1) (hereinafter "EPC"); Agreement on Trade-Related Aspects of Intellectual Property Rights (1994) articles 28 and 33 (hereinafter "TRIPS").

37 MacQueen, Hector et al., Contemporary Intellectual Property Law and Politics, 2nd edition, 2011, Oxford University Press, p. 372.

38 EPC, article 4.

39 Ibid, articles 52–55 and 56.

40 Ibid, article 83.

41 EPC, articles 2-3.

42 Explanatory Memorandum, supra n 10, § 6.

43 Ibid, § 15.

44 SPC Regulation, supra n 9, recital 7.

45 Council Regulation (EEC) No 1768/92, supra n 15.

46 SPC Regulation, supra n 9.

47 Ibid, recitals 3-6.

48 Explanatory Memorandum, supra n 10, recital 3.

49 Ibid, recital 7.

50 Ibid, recital 9.

51 Ibid, recital 10.

The SPC is a *sui generis* right granted through an application process as a successor to a patent. The extension via a Supplementary Protection Certificate is governed by an EU Regulation and is intertwined with both patent and regulatory law. The legislative basis is harmonized under European law, however since patent law has not yet been harmonized on a European level, the SPC confers national protection – hence, it is the national patent law which must be applied within the context of the SPC Regulation.

The SPC regime in the EU does not strictly speaking extend patent term. Instead, it confers a separate right which is meant to be open to the same challenges of validity as an already granted patent ("the basic patent") and to be capable of enforcement in the same way as the basic patent, except that its scope is limited to the particular product that is protected by that basic patent and which has also received its first marketing authorization.[52]

One reason for this approach lies in the fact that the SPC regime is a creature of EU law, in contrast to patents which are subject to the European Patent Convention, which is not an EU instrument, and which did not at the time of the SPC Regulation admit the possibility of patent term extension. The amendment to the EPC to permit patent terms of more than 20 years from the date of filing first came into effect on 4 July 1997.[53]

Any medicinal product protected by a patent in force in the territory of a member state may be the subject of an SPC.[54] Article 3 of the SPC Regulation sets out the conditions which must be fulfilled in respect of the product in order to obtain an SPC including that a basic patent is in force, a valid marketing authorization exists and is the first such authorization, and that the product has not already been awarded an SPC. An application for an SPC must be lodged within six months of obtaining the marketing authorization to place the product on the market.[55]

An SPC is a "national document harmonized at the Community level and is essentially different from the basic patent."[56] Therefore, the national industrial property office in each member state is responsible for assessing and granting SPCs.[57] It provides for the same rights that are conferred by the basic patent for which the SPC is based upon, and is subject to the same limitations and obligations.[58]

According to EU Law, national courts must interpret the SPC Regulation in the same manner as the CJEU.[59] Faced with a dilemma, the national court must pause the national proceedings in order to refer for a preliminary ruling to the CJEU under Article 267 of the Treaty of the Functioning of the European Union (hereinafter "TFEU").

The interpretation of the law governing an additional period of protection after the expiration of the patent term attained through an SPC is complex. The issue that is often raised in case law has been centered on Article 3(a) of the SPC Regulation, one rule transplanted from the Hatch-Waxman Act, which requires that the product be protected by a basic patent in force.

4.0 INTERPRETATION OF A "PRODUCT PROTECTED BY A PATENT"

4.1 U.S. Case Law

The restoration of a patent term in the U.S. is available for a new product, meaning the active ingredient of a new drug.[60] However, a new drug application does not always qualify for patent term restoration.

An early case clarifying the scope of the term *product* in this context was *Fisions plc v Quigg*,[61] where an application for an extension covering a new dosage formula was rejected and the Court of Appeals for the Federal Circuit (hereinafter "CAFC") ruled that product refers to the active ingredient. Another case, *Arnold Partnership v Dudas*[62], stipulated that a new combination of old drugs, or a new use of old drugs, failed to qualify as a new product.

The U.S. Patent and Trademark Office (PTO) initially interpreted the term *product* in Section 156(a)(5)(A) to mean "active moiety," meaning the molecule in a medicinal product responsible for the pharmacological action (regardless of whether the active moiety is formulated as a salt, ester, or other noncovalent derivative), as opposed to an "active ingredient", which is physically found in the medicinal product.[63]

However, in 1990 the Court of Appeals ruled in the case of *Glaxo Operations UK Ltd v Quigg* that an ester of a previously approved salt was in fact a new product and entitled to an extension.[64] In *PhotoCure ASA v Kappos*,[65] the Federal Circuit rejected the "active moiety" argument by the PTO and held that the term product means the active ingredient present in the drug for which the marketing approval was obtained. The court noted that the patent term restoration statute was enacted to restore a portion of the patent life lost during the lengthy procedures associated with the FDA's regulatory review, with the goal to preserve the economic incentive for development of new therapeutic products.

In the current revision of the Hatch-Waxman Act, the term product is defined as a new drug "...including any salt or ester of the active ingredient, as a single entity or in combination with any other active ingredient."[66] The FDA now also clearly states that a new ester or salt of a previously approved acid is eligible for patent extension, while a new acid of a previously approved salt or ester is ineligible.[67]

The Federal Circuit court ruled in *Hoechst-Roussel Pharm., v Lehman*[68] that at least one claim of the patent must claim the approved product, method of using the approved product, or method of manufacturing the approved product. In *Merck v Teva*,[69] an extension was granted for a salt of an acid, as the definition of product in Section 156(a)(5)(A) includes salt or ester.[70]

For a medicinal product that contains more than one active ingredient, the Federal Circuit has held that at least one of the claimed active ingredients (including any salt or ester of that active ingredient) must be new to the marketplace as a medicinal product for a patent covering the medicinal product to be eligible for patent term extension.[71]

4.2 EU Case Law

The SPC Regulation operates at the interface between two different ecosystems - the laws and practices of the patent system to protect inventions, and the marketing authorization procedures of the pharmaceutical regulatory system to protect the consumer. The subject matter of protection under an SPC, the *product*, is linked to both the patent and marketing authorization, extending only to the product as covered by the marketing authorization within the limits of the protection conferred by the basic patent.[72]

The interpretation of Article 3(a) of the SPC Regulation requires a statutory definition of a "product" in the context of Article 1(b) of the SPC Regulation.

4.2.1 Definition of Product

The definition of *product* is central to the operation of the provision of the SPC Regulation and has proven to present difficulties when attempting to apply the substantive provisions of the regulation. A *product* is defined in Article 1(b) of the SPC Regulation as "the active ingredient or combination of active ingredients of a medicinal product[73] and the term should be subject to a narrow interpretation.[74]

The CJEU has determined that the following are not active ingredients, and therefore not "products":

- An inert excipient which has no therapeutic effect on its own used to obtain a certain pharmaceutical form yet is required to make the active ingredient therapeutically effective.[75]
- An inactive carrier.[76]
- An adjuvant.[77]
- An active ingredient which acts only as an adjuvant when in combination with another active ingredient to which it is covalently bound, meaning it does not in the given situation produce a pharmacological immunological or metabolic action of its own which is covered by the therapeutic indications of the marketing authorization.[78]

The CJEU has also held that the following are not different active ingredients in relation to the question of multiple SPCs and therefore not different "products":

- The product, as a medicinal product, in any of the forms enjoying protection of the basic patent. Specifically, salts and esters of a product are not separate active ingredients.[79]
- A purer form or different concentration of the active.[80]

4.2.2 Article 3(a) of the SPC Regulation

The interpretation of Article 3(a) of the SPC Regulation of whether or not a product is protected by a basic patent in force has elicited a substantive number of disputes and jurisprudence at the CJEU.

Prior to the landmark *Medeva*[81] case (along with a rapid succession of related case rulings building upon its reasoning which came to be known as the Medeva quintet[82]) national courts of EU member states pursued one of two methods in interpreting Article 3(a) - the "infringement test" or the "identification or disclosure test."

52 Cook, Trevor, The Court of Justice Recasts the EU Patent Term Extension System, Journal of Intellectual Property Rights, March 2014, volume 19, p. 141.
53 The Act Revision Article 63 EPC of 17 December 1991 (OJ EPO 1992), p. 1.
54 SPC Regulation, supra n 9, article 2.
55 Ibid, article 7. Note that if the MA is obtained prior to the patent, then the application for an SPC must be lodged within 6 months of the grant of the patent.
56 Explanatory memorandum, supra n 10, p. 12.
57 SPC Regulation, supra n 9, article 9.
58 SPC Regulation, supra n 9, article 5.
59 See cases C-6/64 Costa v. Enel ECLI:EU:C:1964:66, Case C-106/77 Simmenthal ECLI:EU:C:1978:49, Case 26/62 Van Geht en Loos ECLI:EU:C:1963:1, Case C-399/11 Melloni, ECLI:EU:C:2013:107 and Case C-617/10 Aker Fransson ECLI:EU:C:2013:105.
60 Title 35 of the United States Code § 156(f).
61 10 USPQ2d 1869 (CAFC 1989).
62 362 F.3d 1338 (Fed. Cir. 2004).
63 See Glaxo Operations UK Ltd. v Quigg, 894 F.2d 392 (Fed. Cir 1990).
64 13 USPQ2d 1628 (CAFC 1990).
65 603 F.3d 1372 (Fed. Cir. 2010).
66 Title 35 United States Code 156(f)(1)(A) and 156(f)(2)(A).
67 www.fda.gov/cder/about/smallbiz/patent_term.htm, 14 February 2018.
68 109 F.3d 756 (Fed. Cir. 1997).
69 347 F.3d 1367 (Fed. Cir. 2003).
70 See Glaxo Operations UK Ltd v Quigg 894 F.2d 392 (Fed. Cir 1990).
71 See Arnold Partnership v. Dudas, 362 F.3d 1338 (Fed. Cir. 2004).
72 SPC Regulation, supra n 9, article 4.
73 SPC Regulation, supra n 9, article 1(b).
74 Explanatory Memorandum, supra n 10, p. 16.
75 C-431/04 MIT ECLI:EU:C:2006:291.
76 C-202/05 Yissum ECLI:EU:C:2007:214.
77 C-210/13 Glaxosmithkline ECLI:EU:C:2013:762.
78 C-631/13 Forsgren ECLI:EU:C:2015:13.
79 C-392/97 Farmitalia ECLI:EU:C:1999:416.
80 C-258/99 BASF ECLI:EU:C:2001:261.
81 Case C-322/10 Medeva BV v Comptroller General of Patents, designs and Trade Marks, ECLI:EU:C:2011:773. (hereinafter Medeva).
82 C-322/10 Medeva BV ECLI:EU:C:2011:773, C-422/10 Georgetown University ECLI:EU:C:2011:776, C-518/10 Yeda Company Ltd and Aventis Holdings Inc. ECLI:EU:C:2011:779, C-630/10 University of Queensland and CSL Ltd ECLI:EU:C:2011:780 and C-6/11 Daiichi Sankyo Company ECLI:EU:C:2011:781.

The "infringement test" is a relatively wide test interpreting Article 3(a) as extending to anything under which an action for infringement could be successfully brought under the national court by looking at whether the product under the SPC would infringe upon the basic patent. The "identification or disclosure test" applies a narrower interpretation of the provision in which a patent claim must sufficiently disclose the relevant product in order for the patent protection to cover it.[83]

The decision of the CJEU in *Medeva* held that an SPC could be granted if the active ingredient or ingredients are specified in the wording of the claims of the basic patent and furthermore explicitly rejected the infringement test.

The Medeva case, referred to the CJEU by the United Kingdom (UK), concerned a patent owned by Medeva for two active ingredients in a whooping cough vaccine, pertactin and filamentous heamagglutinin (Hg). The patent was filed in 1990, granted in 2009 and expired in 2010. The first commercial vaccine using their active ingredients was given marketing authorization in 1996 in combination with other ingredients.

In 2009, Medeva applied for five SPCs to seek protection for a new combinatory vaccine holding a marketing authorization and covering respectively diphtheria (D), tetanus (T), Bordetella pertussis (Pa), poliomyelitis (IPV) and/or haemophilus influenza (HIB). The respective vaccines all contained the combination of Medeva's patented active ingredients pertactin and Hg, together with 8 to 11 other active ingredients.

All five SPC applications were rejected because although the respective vaccines included pertactin and Hg as specified in the basic patent, they were included in combination with other active ingredients not covered by the claims of the basic patent. The court found that the products did not fall under the protection of the basic patent according to Article 3(a), as they covered more active ingredients than were referred to in the subject matter of the basic patent.[84] An appeal was lodged and because the High Court had doubts with regard to the interpretation of Article 3(a), it referred a number of questions to the CJEU for a preliminary ruling under Article 267 TFEU.

The key question referred by the Court of Appeal was:

What is meant in Article 3(a) of the Regulation by "the product is protected by a basic patent in force" and what are the criteria for deciding this?

The Opinion of the Advocate General[85] (hereinafter "AG") delivered on 13 July 2011 became an important platform for the interpretation of Article 3(a) of the SPC Regulation.

The first step in the interpretation by the AG was a literal approach based on the wording and scheme of the Regulation, which led the AG to conclude that the definition of a product in Article 1(b) must be interpreted to mean the entire combination of active ingredients as such, not just the patented parts.[86] The AG reasoned that on a literal interpretation of the wording "only the combination of active ingredients of that medicinal product in its entirety, and not the patented part of that combination, can be described as a product within the meaning of Article 1(b)."[87] The opinion continued with the notion that a literal interpretation ..."leads to the conclusion that, in the case of medicinal products with multiple active ingredients, that an SPC may be granted only in the relation to the entire (patented) combination of the active ingredients."[88]

The AG concluded that a literal interpretation of Articles 1(b) and 3(a) was therefore not compatible with the aim of the Regulation to extend the term of patent protection for active ingredients used in medicinal products, as it would create a situation where it would never be possible to extend a term of patent protection when a manufacturer is obliged to combine their patented active ingredient with others to market it as a medicinal product.[89]

The AG then applied a teleological interpretation "proceeding with great caution" in consideration of the goal to achieve a balance between the various interests at stake in the pharmaceutical sector - a complex situation.[90] After, AG undertook an exercise in teleological reasoning, with the result that a combination of patented and non-patented active ingredients would in fact fall within the scope of Article 3(a) of the SPC Regulation.[91] The AG acknowledged that this would introduce a risk that a manufacturer could abuse the system by combining different active ingredients on the basis of one patented active ingredient, and therefore concluded that only one SPC could be granted on the basis of a product that is the subject matter of the basic patent.[92]

The question of whether the product is the subject matter of the basic patent is then to be determined by the national laws governing the patent. However, the AG stated that it was incompatible for a national court to "invoke the protective effect of the patent granted for a specific ingredient in order to declare that patent to be the basic patent for all combinations of active ingredients in which the patented active ingredient was to be used."[93] In this interpretation the AG distinguishes between the subject matter of a basic patent and its protection.

The AG cited that the reason for rejecting the infringement test under Article 3(a) was the fact that the patent claim scope is not harmonized at an EU level, and so the concept should be given an autonomous meaning. Thus, the AG held that for an active ingredient to be "protected by a patent" that such active ingredient must be "specified" or "identified" in the wording of the claims of the basic patent.

In its judgment, the CJEU followed the opinion of the AG by stating that to assess whether or not Article 3(a) was fulfilled, the patent claims should be examined to see if the active ingredients are specified in the wording of the claims. It also emphasized that Article 3(a) of the SPC Regulation must be interpreted as precluding the competent industrial property office of a member state from granting an SPC relating to active ingredients which are not specified in the wording of the claim of the basic patent relied on in support of the SPC application.[94]

Critics have claimed this approach to Article 3(a) may reflect ignorance on the part of the CJEU which has little experience of the variety of different ways in which patent claims to pharmaceuticals may be formulated, and that the judgment immediately put into question the issue of whether SPCs could be secured for single active products where there are not relevant claims of the basic patent that list specific chemicals, but only that the relevant claims are expressed functionally as a "Markush" form.[95]

This issue was addressed by the CJEU two years later in *Eli Lilly v Human Genome Sciences*[96] which held that to be treated as protected it was not necessary for the active ingredient to be identified in the claims of the patent by a structural formula, but that it had to be possible for someone skilled in the art "to reach the conclusion on the basis of those claims, interpreted inter alia in the light of the description of the invention (...) that the claims relate, implicitly but necessarily and specifically, to the active ingredient in question."[97] The CJEU suggested that Article 3(a) would not be met in circumstances "where the patent holder has failed to take steps to carry out more in-depth research and identify his invention specifically" – meaning that specific indication in the claims of all ingredients is a prerequisite for protection.[98]

There have been a number of CJEU decisions discussing the meaning of a "product protected by a basic patent" yet these decisions have not provided a generally applicable test for meeting the condition of Article 3(a).

The guidance given by the CJEU on the relationship between the product and the patent to date can be summarized as follows:

- All active ingredients in the product must be specified[99] or identified[100] in the wording of the claims of the basic patent for a product claim patent. In the case of a process claim, all active ingredients in the product must be identified in the wording of the claims of that patent as the product deriving from the process in question.[101]
- An active ingredient (A) which is identified in the wording of the claims of the basic patent as an active ingredient forming part of a combination with another active ingredient (A+B), but which is not the subject of any claim relating to the active ingredient alone, is not protected by the basic patent.[102]
- It is not necessary for the active ingredient in the SPC to be identified in the claims of the patent by a structural formula. However, where the active ingredient is covered by a functional formula, the claims need to relate "implicitly but necessarily and specifically "to the active ingredients in question. The application of that test to the facts is a matter for the national courts.[103]
- The claims are of central importance when determining whether a product is protected by a basic patent. An active ingredient which is not identified in the claims of a basic patent by means of a structural or a functional definition cannot be protected within the meaning of Article 3(a).[104]
- The question of whether or not the product is protected by a basic patent must ultimately be determined by reference to the national rules governing the patent in question[105] but note that recourse should not be given to national infringement rules when considering Article 3(a).[106]

The word "identified" was used instead of the word "specified" in several cases.[107] The difference in wording was not addressed by the CJEU and it is unclear whether it was deliberate, and whether or not it is significant.

83 Miller, Richard, et al., Terrell on the Laws of Patents, 17th edition 2011, p. 144.
84 Medeva BV v The Comptroller General of Patents (2010) EWHC 68 (Pat) (Medeva EWHC); AG Opinion in Medeva, supra n 8, para. 15–17.
85 AG Opinion Medeva, supra n 8.
86 Ibid, para. 63.
87 AG Opinion Medeva, supra n 8, para. 67.
88 Ibid, para. 63.
89 Ibid, paras. 75 and 80.
90 Ibid, paras. 77–78.
91 Ibid, paras. 89–90.
92 Ibid, para. 100.
93 AG Opinion Medeva, supra n 8, para. 72.
94 Medeva, supra n 84, para. 28.
95 Cook, supra n 52, p. 143.
96 C-493/12 Eli Lilly v Human Genome Sciences ECLI:EU:C:2013:835.
97 Ibid, para. 39.
98 Ibid, para 43.
99 C-322/10 Medeva ECLI:EU:C:2011:773.
100 C-518/10 Yeda ECLI:EU:C:2011:779.
101 C-630/10 Queensland ECLI:EU:C:2011:780.
102 C-518/10 Yeda ECLI:EU:C:2011:779.
103 C-493/12 Eli Lilly ECLI:EU:C:2013:835.
104 Ibid.
105 C-392/97 Farmitalia ECLI:EU:C:1999:416.
106 C-493/12 Eli Lilly ECLI:EU:C:2013:835.
107 C-518/10 Yeda ECLI:EU:C:2011:779, C-630/10 Queensland ECLI:EU:C:2011:780, C-6/11 Daiichi ECLI:EU:C:2011:781.

5. MATERIAL WEAKNESS OR INSTITUTIONAL INEFFICIENCY?

5.1 The Donor Rule

The legislative intent of the Hatch-Waxman Act was to achieve a delicate balance of innovation and competition. Many conclude that the Hatch-Waxman Act did encourage growth in the generic sector and provided brand companies with incentives. However, these incentives led to gaming of the system. Both brand name and generic companies evolved in their strategy towards patent term extensions.[108] Brand companies discovered loopholes and generic companies developed their own anticompetitive strategies to level the playing field.[109]

Early on, litigation ensued to resolve the ambiguity and construe the statutory meaning of terms such as "active ingredient" and "product."[110] Despite attempts to clarify this issue, conditions for patent term restoration remained the subject of controversy and as a result, the Hatch-Waxman Act was amended.[111]

An analysis in the Berkeley Technology Law Journal claims patent term restoration is unpredictable – "fluctuating from product to product, over time, and based on the type of treatment and illness."[112] Furthermore, the article claims that patent term restoration has failed to align the incentives of the pharmaceutical industry with public health, as the brand names have responded to the incentives by increasing their reliance on improvement patents which represent an "inefficient run-around" to the system.[113]

That same article claimed the history and structure of the Hatch-Waxman Act as being plagued with contradictory and extraneous provisions that resulted in an unpredictable, biased, and innovation-suppressing patent-term restoration system.[114] The article goes so far as to draw the conclusion that "major structural reforms are needed" due to the fact that "the life of a pharmaceutical patent continues to be highly unpredictable and subject to numerous biases and inefficiencies."[115]

The Hatch-Waxman Act has been referred to by the court as "an ambitious piece of legislation (...) by no means a model of legislative clarity."[116] The U.S. lawmaking institutions and the pharmaceutical industries' "race for patents" has resulted in considerable litigation as the courts and the FDA have sought to interpret the Hatch-Waxman Act in a way that is consistent with both the statutory and legislative intent. While some maintain that the federal court system has adequate authority to challenge litigation settlements that may be anticompetitive, others believe the judicial system is not the appropriate venue to resolve these issues.[117]

5.2 The Recipient Legal System

The EU adopted provisions for the SPC Regulation following the initial enactment of the Hatch-Waxman Act, transplanting the discourse over the conditions under which an SPC may be granted. Article 3(a) has been a disputed issue in granting an SPC, *a sui generis* right that "lies at the interface between two systems."[118]

The AG in *Medeva* points out an internal conflict of the wording itself due to the definitions of "medicinal product", "product" and "active ingredient" attempting to bridge the gap between the spheres of pharmaceutical law and intellectual property law. The AG highlights a number of inconsistencies and ambiguities in the definitions, which require a clear interpretation and yet it is not always clear to what extent these terms are intended to co-exist in content.[119]

One of the most controversial questions in the dispute has long been how to define whether a product is protected by a basic patent in force.

On 24 November 2011, the CJEU delivered its judgments in *Medeva*[120] and *Georgetown I*,[121] and only one day later, the *Queensland*,[122] *Yeda*,[123] and *Daiichi Sankyo*[124] decisions were delivered, all of which followed the court's reasoning in *Medeva* and *Georgetown*.

The decisions in the "Medeva Quintet" established a precedent, however it did not clarify what level of identification or specification is required for the product to be considered the subject matter of a basic patent. This was later addressed in a series of judgments delivered two years later in the cases of *Actavis*,[125] *Georgetown II*[126] and *Eli Lilly*[127] which are often referred to as the "Lilly Trio".

Although the judgments in the Lilly Trio attempted to build upon the Medeva Quintet,[128] the clarification brought by the CJEU in the Lilly Trio did not address all the controversial issues in the interpretation of Article 3(a)[129] and introduced yet another test difficult for national patent offices to apply to cases having different material facts.

The "one SPC for one patent" restriction in the *Medeva* opinion[130] has been the topic of contention as it is deemed inconsistent with practice. In the AG Opinion of the earlier Biogen case[131] from 1996, the AG stated that "it is nowhere stated that a patent can be the subject of only one certificate, or of a certificate in respect of one medicinal product, as the same patent may be used for widely differing medicinal products."[132]

The Commission specifically states in their Explanatory Memorandum that the Regulation concerns only new products and only one certificate may be granted for any one product - a product being understood to mean an active substance in the strict sense. Minor changes to the medicinal product will not lead to the issue of a new certificate.[133] The Commission does not state "one SPC for one patent" instead "one SPC for one product."

Although the main principles are embedded at the Community level in the SPC Regulation, the national industrial property office in each member state is responsible for assessing if the product in question is protected by a patent. This means that when the courts attempt to interpret the SPC Regulation, significant weight is given to the purposes and rationales set out in the recitals and the general principles of the SPC Regulation.[134] Adding to the complexity of the SPC Regulation is that the national interpretation is made in the same tribunals as patents, which must also employ concepts drawn from other institutions competence areas such as regulatory law and the marketing authorization regime.

In the recent UK case of *Teva v Gilead*,[135] the Judge said in paragraph 81:

> *I am bound to say that...the Court of Justice has once again failed to give national authorities clear guidance as to the proper interpretation of Article 3(a).*

The judge then stated in paragraph 91:

> *In my judgment the test to be applied in order to determine whether a product is "protected" by a basic patent within the meaning of Article 3(a) remains unclear. It is clear that it is not sufficient that dealings in the product would infringe a claim applying the Infringing Act Rules. It is also clear that it is necessary that the product falls within at least one claim of the basic patent applying the Extent of Protection Rules. But it is not clear whether that is sufficient. It appears from the case law of the CJEU that it is not sufficient, and that more is required; but it is not clear what more is required. Accordingly, it is necessary to refer the question once more to the Court of Justice in the hope that finally a clear answer will be given.*

The Judge concluded by stating:

> *I shall therefore ask (question 1 in Actavis v Sanofi) again: What are the criteria for deciding whether "the product is protected by a basic patent in force" in Article 3(a) of the SPC Regulation?*

6. CONCLUSIONS

It seems reasonable to conclude that the SPC Regulation fails to meet one of its fundamental objectives to provide a "simple, transparent system which can easily be applied by the parties concerned."[136]

It is clear that the evolution of medicinal products and the intense competition of the pharmaceutical industry bring challenges to the application of the SPC Regulation, in particular with regards to the definition of the subject matter of an SPC[137] – a product protected by a patent. The means by which an SPC is achieved is a matter of EU law and must ultimately be interpreted by the national courts in the manner of the CJEU, and consequences of any preliminary rulings must be implemented by national courts.[138]

[108] Rumore, Martha M., The Hatch-Waxman Act – 25 years later: Keeping the Pharmaceutical Scales Balanced (2009).
[109] Bajefsky RD, Chopskie G., Biting the Hand that Feeds? Generic Drugs and Abuse of the Hatch-Waxman Law, Washington Legal Foundation, 2002, 17:1.
[110] McGough KJ., Preserving the Compromise: The Plain Meaning of Hatch-Waxman Market Exclusivity, Food Drug Cosmetic Law Journal, volume 45, pp. 487-504.
[111] Medicare Prescription Drug Improvement and Modernization Act of 2003. Publ L. No. 108-173, 117 Stat. 2066 (2003).
[112] Cárdenas-Navia, James F., Thirty Years of Flawed Incentives, Berkeley Technology Law Review, 2014, volume 29, p. 1373.
[113] Ibid, p. 1374.
[114] Cárdenas-Navia, supra n 112, p. 1373.
[115] Ibid, p. 1301.
[116] Eli Lilly v. Medtronic, Inc. 496 U.S. 661, at 649 (1990).
[117] Rumore, Martha M., The Hatch-Waxman Act – 25 years later: Keeping the Pharmaceutical Scales Balanced (2009).
[118] Explanatory Memorandum, supra n 10, para. 20.
[119] AG Opinion Medeva, supra n 8, para. 58.
[120] C-322/10 Medeva ECLI:EU:C:2011:773.
[121] C-422/10 Georgetown ECLI:EU:C:2011:776.
[122] C-630/10 University of Queensland ECLI:EU:C:2011:780.
[123] C-518/10 Yeda ECLI:EU:C:2011:779.
[124] C-6/11Daiichi ECLI:EU:C:2011:781.
[125] C-443/12 Actavis ECLI:EU:C:2013:883.
[126] C-484/12 Georgetown ECLI:EU:C:2013:828.
[127] C-493/12 Eli Lilly ECLI:EU:C:2013:835.
[128] Gassner, U.M., Recent development in the area of supplementary protection certificates, Pharmaceutical Policy and Law, 2016, volume 16, p. 58.
[129] Papadopoulou, Frantzeska, Supplementary protection certificates: still a grey area?, Journal of Intellectual Property Law & Practice, 2016, volume 11, no 5, p. 376.
[130] Opinion Medeva, supra n 8, paras. 98–101.
[131] C-181/95 Biogen v Smithkline Beecham ECLI:EU:C:1996:370.
[132] Opinion on Case C-181/95 Biogen Inc v SmithKline Beecham Biological S.A. (1996) ECLI:EU:C:1996:370, para. 53.
[133] Explanatory Memorandum, supra n 10, p. 8.
[134] Richard Miller, et al., Terrell on the Laws of Patents, 17th ed. (2011) p. 144.
[135] Teva UK Ltd and Ors v Gilead Sciences Inc (2017) EWHC 13 (Pat).
[136] Explanatory Memorandum, supra n 10, para 16.
[137] Papadopoulou, supra n 129, p 373.
[138] Cook, supra n 52, p. 141.

The aim of preventing a heterogeneous development of national laws to ensure a uniform solution within the Community carries significant weight when interpreting the Regulation.[139] However the AG states in the *Novartis* case that an analysis of the recitals in the SPC Regulation indicate that the main objective of the legislature was not to guarantee the free movement of medicinal products within the Community, but to ensure that conditions exist for profitable pharmaceutical research and to deter firms from relocating outside the union.[140]

The CJEU is forced to maneuver within the complex linkage between the EU SPC Regulation, the national patent law and courts of the member states, as well as the market authorization process of the European Medicines Agency – interpreting terminology that is uncoordinated across the three systems.[141]

During the literal interpretation exercise in the *Medeva Opinion*, the AG discussed internal conflicts of the wording of the SPC Regulation.[142] The provisions of the SPC Regulation adopted from the Hatch-Waxman Act brought with it the same basic flaws. Notwithstanding the material law itself, the institutional law-making system in the EU introduces new weaknesses, creating legal uncertainty in the application of the SPC Regulation.

In the EU legal environment, patent law is not (yet) harmonized and the law-making court (CJEU) is unable to rule on the interpretation of the EPC, as the EU is not party to the EPC.[143] Lacking jurisdiction to interpret the provisions of the EPC, the Court cannot provide further guidance to the referring court concerning the manner in which it is to determine the extent of the claims of a patent issued by the EPO.[144]

As a result, the CJEU with its limited competence to interpret patent law is faced with the challenge of interpreting the SPC Regulation in a manner consistent with its objectives, without jeopardizing the balance between the various interests at stake.[145] In 2014 it was written: "When a national court makes a referral because there is a particular area of uncertainty, a judgment from the CJEU follows that fails to clarify the original uncertainty, and creates a new one."[146] An unequivocal ruling by the CJEU is needed to allow national courts to avoid divergence in their conclusions. However, The CJEU may be correct in their reluctance, as the court does not have the jurisdiction to interpret EPC provisions.[147]

In the end, the final conclusion of whether a product is protected by a patent is left to the national courts, armed solely with the CJEU reference to Article 69 EPC in combination with the conclusion that the claims should relate "implicitly but necessarily and specifically" to the active ingredient in question. The determination of whether the subject matter falls within the scope of the patent turns out to be a rather complicated task.[148]

The lack of EU harmonization on substantive patent law contributes to the fragmented application of the SPC Regulation.[149] The interdependence between three systems in the EU introduces complexity beyond the material application of the rule in comparison with the U.S. where patent and patent term extensions are processed within the same courts, and where both patent extensions and marketing authorization are part of the same body of legislation. This arrangement presents advantages, including consistent use of technical terminology and coherence in the system as a whole.[150]

[139] Teva UK Ltd and Ors v Gilead Sciences Inc (2017) EWHC 13 (Pat), p. 145.
[140] AG Opinion in joined cases C-207/03 and C-252/03 Novartis AG, University College London and Institute of Microbiology and Epidemiology v Comptroller, ECLI:EU:C:2004:491, para. 42.
[141] Papadopoulou, supra n 129, p. 380.
[142] AG Opinion Medeva, supra n 8, paras. 57 – 62.
[143] According to the European Patent Convention, adopted by the Administrative Council or the European Patent Organization by decision of 28 June 2001.
[144] C-493/12 Eli Lilly ECLI:EU:C:2013:835, para. 40.
[145] Cook, supra n 52, p. 141.
[146] Smyth, Darren, Two gaps instead of one: the CJEU's effect on Supplementary Product Certificate jurisprudence, Journal of Intellectual Property Law & Practice, 2014, volume 9, no 6, p. 445.
[147] C- 493/12 Eli Lilly ECLI:EU:C:2013:835, paras. 39–44.
[148] Papadopoulou, supra n 129, p. 376.
[149] Ibid, p. 373.
[150] Ibid, p. 381.
[151] Cárdenas-Navia, supra n 112, p. 1375.
[152] Ibid, p. 1377.

The potential of the Unitary Patent Package (UPP) may improve the system coherence, however it may create yet another fissure in an already fragmented system as current European patent holders are given the option to "opt out" of the UPP system. The EU legislature may consider amending the wording of the Regulation to support a homogenous interpretation by the national courts and fulfill the purpose of the SPC Regulation.

One alternative to an amendment of the rule would be to automatically restore any patent time lost during regulatory approval up to the limit. It is argued that guaranteeing a minimum term of exclusivity for new products would provide the predictability to effectively promote pharmaceutical research and "allow brand names to focus on competing against one another instead of against their patent term clocks, eliminating inefficiencies."[151]

Another solution would be to eliminate patent term extensions, focusing instead on terms of market exclusivity. Market exclusivity would ensure that generic manufacturers could not enter the market until a certain number of years have passed after the brand-name product entered the market. A major advantage of market exclusivity compared to patent term extensions is its ease of enforcement, taking away the requirement of a case-by-case analysis on the patent claim construction.[152]

The EU legal system, with the CJEU lacking the competence to rule on patent law, will suffer from incoherence while national courts continue to face legal uncertainty when determining whether the product implicitly but necessarily and specifically is identified or specified in the patent claim.

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The patentability of Dosage Regimes:

How to receive and enforce Dosage Regimes patents in Europe

By Ester-Maria Elze

ABSTRACT

Despite the therapeutical benefits of dosage regimes, being granted and securing patent protection for these types of inventions has always been difficult. Historically dosage regimes have generally been excluded from patent law as these were held to either lack industrial application or were caught by the medical methods exclusions arguing that these inventions unjustifiably limited the medical profession's choice of clinical practices. In 2010, the Enlarged Board of Appeal of the European Patent Office however held that dosage regimes are no longer excluded as such under the European Patent Convention 2000. In the post-EPC 2000 era the challenge is instead for dosage regimes to fulfill the requirements of novelty and inventive step. In seeking to bring greater clarity to the field of dosage regimes, this article aims at establishing what is required in order to be granted and enforce dosage regimes patents in Europe. In order to offer strategies to practitioners and potential patentees in regards to litigation as well as Research & Development tailoring, this article additionally contributes to the existing literature by providing for the first time, an empirical study of dosage regime patent decisions of the European Patent Office.

1. INTRODUCTION

Once a new active ingredient has been discovered, much information of its properties and pharmacokinetics[1] are unknown, even after all three clinical trial phases. Knowing more about the different parameters of its pharmacokinetics (drug absorption, drug distribution, drug metabolism and drug excretion) allows dosage regimes to be altered or developed. These adjusted regimes can then increase the efficacy of the drug as well as reduce its toxicity and side effects[2], making the drug effective and suitable for a larger proportion of the population. Whilst generic imitation has remained inexpensive and fast, drug discovery and development has become a longer and costlier process[3], enhancing the increasing need for providing incentives for the latter. For dosage regimes, the market and data exclusivity granted through the Marketing Authorisation Directive[4] does not provide an adequate incentive. This directive covers only active ingredients and offers an only 1-year extension of the existing exclusivity of the active ingredient by 1 year for second medical uses. This means that where more than one second medical uses exist, only the first will be rewarded through the directive.[5]. Solutions must be found elsewhere, such as in patent law.

Only in 2010, the Enlarged Board of Appeal (hereafter EBA) of the European Patent Office (hereafter EPO) attempted in Dosage regime/ABBOTT RESPIRATORY[6] to clarify the legal position of dosage regimes within the framework of the European Patent Convention 2000 (hereafter EPC). Whilst theoretically, it was decided that dosage regimes are patentable as long as these meet the requirements of inventive step and novelty, the position in practice remains nevertheless highly uncertain and unclear. This is enhanced further due to the uncertainty related to the ability and chances of succeeding in enforcing these types of patents through infringement proceedings in the unharmonized, post-grant landscape of the EPC. The EBA has not contributed with a definition of the term "dosage regimes.[7] This becomes even less straight forward because both in literature and different jurisdictions around Europe, different definitions of dosage regimes can be distinguished. For the purpose of consistent analysis, this article will, therefore, adopt the following widely used definition:

> *"Dosage regimes are decisions of drug administration regarding the formulation, route of administration, drug dose, dosing intervals and treatment duration".*[8]

Unfortunately, dosage regimes patents have never attracted much attention from scholars[9], other than with regards to their potential relationship to the controversial concept of "ever-greening". In seeking to bring greater clarity to the patentability of dosage regimes for practitioners, this article seeks to answer the desired question: "How can one receive, protect and enforce a dosage regime patent in Europe?" It, therefore, contributes to the existing literature by offering an in-depth analysis of EPC dosage regimes patents pre- and post-grant. Furthermore, this article offers for the first time an empirical study of EPO granted and refused dosage regime patents analysing the current position of these in practice.

2. THE PATENTABILITY OF DOSAGE REGIMES

2.1. Historical development of dosage regimes as a further medical use patent

At first, due to the adopted literal reading of the EPC, the EPO was reluctant to grant patents for any further medical uses. Whilst the Technical Board of Appeal (hereafter TBA) reiterated in Hoffman-la Roche/Pyrrolidine derivatives[10] that, only the first medical use was protected through the EPC 1973. In practice further medical uses were protected, however, their protection and accompanying monopoly was granted to the patent owner of the first medical indication patent.[11] A patentee of a new known substance therefore in practice, also had a monopoly for future discoveries of new therapeutic effects. An approach that could negatively impact research on second medical uses of an existing drug. Hence, the EPO's approach could be seen as only considering the new discovery of an active ingredient as valuable pharmaceutical research ignoring the basic principle that molecules may have new medicinal properties.[12] As argued by Barry, "molecules should not be viewed as discrete objects but rather as constituted in their relations to complex informational and material environments".[13]

This interpretation of a wide scope of protection was however, diminished through the EISAI/second medical indication[14] to only cover the actual findings at the time of the patent filing. This was done whilst simultaneously concluding, for the first time, that second and further medical indications are capable of being patented on their own. The EBA, in this case, was concerned with the interpretation and interaction between article 54(5), regarding an exception to the general rule of novelty, and 52(4), regarding methods of treatment of the human body of the EPC 1973.

Even though in regards to the latter the issue was only concerned with "therapeutic methods" due to the EBA's reference to "medical indication" in its interpretation of article 54(5), it could be seen that it was referring not only to therapeutic methods but also other all other medical treatment found in article 52(4). Hence, the judgement had a much wider impact, affecting all types of methods including surgical, diagnostic and therapeutical.[15] Drawing a distinction between first and second medical indications, the EBA concluded that it could not "deduce from the special provision of Article 54(5) that there was any intention to exclude second (and further) medical indications from patent protection other than by purpose-limited product claims."[16] The inclusion of further medical use patents hence, originated out of the EBA's interpretation of the EPC's silence. Firstly, the EBA referred only in its decision to the fact that an intention could be deduced from the legislative history of the articles. However, this is inconsistent with the Munich Diplomatic Conference of 1973. Both the Dutch delegation and the Chairman[17], in response to the delegate of Yugoslavia, had expressly stated that Article 54(5) would apply only at first medical indication uses. With closer examination of the "travaux préparatoires", whilst opinions on second medical indications were divided, the majority was not in favour of their inclusion.[18]

1 Pharmacokinetics Can Be Defined As "The Study Of The Properties Of Drugs And Their Interaction With Living Organisms, Including Viruses" (Eckhard Beubler, Kompendium Der Pharmakologie (Springer Berlin Heidelberg 2018)).

2 Ibid.

3 S Basavaraj And Guru V. Betageri, 'Can Formulation And Drug Delivery Reduce Attrition During Drug Discovery And Development—Review Of Feasibility, Benefits And Challenges' (2014) 4 Acta Pharmaceutica Sinica B.

4 Directive 2001/83/EC On The Community Code Relating To Medicinal Products For Human Use (2001).

5 Justine Pila And Paul L. C Torremans, European Intellectual Property Law (Oxford University Press 2016).

6 G 0002/08 (Dosage Regime/Abbott Respiratory), 19.2.2010.

7 Ibid.

8 Roger L. Williams, 'Dosage Regimen Design: Pharmacodynamic Considerations' (1992) 32 The Journal Of Clinical Pharmacology.

9 S.J.R. Bostyn, 'Personalised Medicine, Medical Indication Patents And Patent Infringement: Emergency Treatment Required' [2016] Intellectual Property Quarterly.

10 T 0128/82, Hoffmann-La Roche (Ep0003602), Board Of Appeal Decision Of Epo, 12.01.1984.

11 "An Inventor Who For The First Time Makes A Known Compound (..) Should Be Rewarded To Cover The Whole Field Of Therapy." T 0128/82, Hoffmann-La Roche (Ep0003602), Board Of Appeal Of Epo, 12.01.1984; Accepted In T 0043/82, Roussel-Uclaf (Ep0003200) Board Of Appeal 16.4.1984.

12 Andrew Barry, Political Machines (Lightning Source 2014).

13 Andrew Barry, 'Pharmaceutical Matters' (2005) 22 Theory, Culture & Society.

14 G 0005/83, Eisai/Second Medical Indication, 05.12.1984; Ecli:Ba:1984:G000583.19841205.

15 Eddy D Ventose, Medical Patent Law (Edward Elgar 2011).

16 Op. Cit, Fn.14 (Para. 22).

17 " (..) A Further Patent Could Not Be Granted If A Second Possible Use Were Found For The Same Substance, Irrespective Of Whether The Human Or Animal Body Was To Be Treated With It." Minutes Of The Munich Diplomatic For The Setting Up Of A European System For The Grant Of Patents, Munich 10 September To 6 October 1973, At Para 54.

18 'Patent Protection For Second And Further Medical Uses Under The European Patent Convention' (2009) 6 Scripted.

Secondly, the EBA itself later referred to this ruling as a "praetorian approach" which was "a special approach to the derivation of novelty".[19] Even though the EBA did not give a definition as to what it meant by "praetorian", this term can be understood in the context of its origin in ancient Roman law.[20] Praetorian law according to Aemilius Papinianus is defined as "... that which in the public interest the praetors (judges) have introduced in aid or supplementation of correction of the ius civile (civil law)".[21] Seen in this light therefore, the EBA can be understood as indicating that EISAI went beyond what was agreed by the EPC 1973.[22] Thirdly, from a theoretical perspective, interpretation of silence is a risky and at times unclear matter. Eskridge, based on US law, illustrated the problems and difficulty of making any inferences from the legislator's silence[23]. Eskridge held that, it is very hard to aggregate preferences in a large group of people as well as to establish the meaning of their votes. From accounts of the diplomatic conference proceedings, it becomes evident that this problem is clearly present with regards to the EPC where reaching a clear voting outcome was often not possible due to different judicial backgrounds, interests and opinions.[24] Where, therefore, an amendment to the text of the Convention was not possible because of very close voting outcomes, this cannot accurately indicate a clear "intention of the legislator" as there may be multiple reasons for the legislator's passivity.[25] Fourthly, other than holding that further medical use patents in principle were patentable, the EBA also held that, "it seems justifiable by an analogy to derive the novelty for the process which forms the subject matter of the type of use claim now being considered from the new therapeutic use of the medicament".[26] However as, when one looks at Swiss-type claims, this means that in regards to novelty, the claim is directed to a process for preparation a product. This would mean that, the invention claimed is a process, however, the purpose limitation is not on this process, which as established formulates the subject matter of the claim but in fact on the product itself. This inconsistency in reasoning, therefore, means that the analogy is neither so clear nor direct as stated by the EBA.[27]

It can, therefore, be concluded that, the act of "creating" second medical use patents was done through an unauthorized extension of the EPC and, therefore should be seen as judicial law making. Even though this perhaps could have been done to meet the demands of the pharmaceutical market or the advances of research, which at the time of the drafting of the EPC was not so obvious (most advances and recognition of the importance of pharmacokinetics only took place in the 1980s and onwards)[28], it does not undermine the fact that the decision has been and still can be criticised for being invalid.[29]

In order to by-pass the problems created through this creative interpretation, the EBA established the so-called "Swiss-claims", which would secure patent protection for further medical use patents. Swiss claims had to fulfil two requirements: (a) the manufacture of a medicament and (b) a new application.[30] These essential requirements set out had the function of defining the patent's scope and novelty. Which types of claims satisfied these requirements, became a burdensome debate that resulted in the ever-extending reach of the EISAI principle.[31]

Dosage regimes have specifically fallen within this group of second medical uses types, where patentability was highly uncertain. In Gastrointenstinal compositions[32], concerning a route of administration[33] and in Liposome compositions/SEQUUS[34], the board held that dosage regimes were not patentable. In the latter it was reasoned, taking a narrow reading of EISAI/second medical indication that, the claims at issue concerning the time and dose of administration were not a method of treatment or therapeutic application with the meaning of article 52(4) of the EPC 1973 but claims related to a process. In "Thiazide diuretics"/EURO-CELTIQUE[35], the TBA held that specifically personalised dosage regimes are not patentable, reasoning that this falls within the sphere of competences of medical practitioners.[36] These decisions ignore however, the substantial input of intellectual and financial resources necessary to produce such regimes, which reach far-beyond what is within the routine of a medical practitioner.[37]

In contrast, the TBA took a completely different approach in Sereno/HCG. Drawing on DUPHAR/pig II[39] and ICI/cleaning plague[40] it concluded that the mode of administration might be a critical factor in a medical treatment, thereby seeing no reason why it should be held that there is no patentability per se without proceeding the assessment of novelty and inventive step. In regards to dosage regimes it could therefore be seen that the EPO was relatively divided and unclear as to their position and their importance as well as to the intellectual input required of dosage regimes. In contrast to second medical indications, the legal landscape of dosage regimes was shaped by great legal uncertainty, disadvantageous for both the patent offices and applicants.[41]

Matters were made even more unclear when it became apparent that multiple interpretations of the EISAI[42] judgement and its relationship to dosage regimes co-existed within the different TBAs. In T1020/03[43] the TBA had held that dosage regimes are patentable inline with Article 52(4). Relying on the statements made in obiter dicta in EISAI[44], according to which new formulations, dosages or synergistic combinations would in principle face no difficulty regarding the question of novelty. Furthermore, it claimed that the expressed views in T317/95[45], T0056/97[46], T0584/97[47], T0485/99[48], rejecting the patentability of dosage regimes, conflicted with the EISAI decision and had no real legal basis in the EPC. Whilst this decision was followed in some cases for example T0515/06[49] and T0708/02[50] in Smithkline Beecham Corporation/Treatment of ovarian cancer[51] the TBA concluded that EISAI was not concerned with the novelty of dosage regimes and its comments could only be taken as obiter dicta. Contradictions amongst the TBAs led to great uncertainty. With the introduction of the EPC 2000, it was beyond doubt that further medical use patents were patentable. However the question of dosage regime specifically was not answered until the TBA in Kos Life Science Inc./dosage regimes[52] referred the question of patentability to the EBA. In contrast to the general approach before, the TBA noted that considerations concerning public health and medical profession confidentiality should not be a primary consideration when interpreting the current law.

In dosage regime/ABBOTT RESPIRATORY[53] the EBA firstly clarified that the change from 52(c) EPC 1973 to article 53(c) EPC 2000 was an editorial and not a substantive change. Furthermore, the EBA was of the opinion that the intention of the legislator in regard to the changes brought to Article 52(4) of EPC 2000 was to enshrine the intentions set out in EISAI/second medical indication[54] and its subsequent case law. It appears contradictory as firstly, the intention and situation was not clear as outlined above and secondly, prior case-law prior to this case actually held that dosage regimes were in fact not patentable.[55] A potential clarification opportunity was therefore in part wasted.

Nevertheless, the EBA in G2/08 clarified that the term "any specific use" should neither be interpreted in a limiting way nor substantially different to 54(5) of the EPC. The EBA, therefore, adopted a wide reading of the provisions 54(4) and 54(5). It however also held that in regard to dosage regimes the freedom of medical practitioners should be protected at a national level, if found necessary. This means that a claim approved by the EPO may, in fact, be in conflict with the laws and restrictions at national level. Through this and the lack of uniform definition of dosage regimes, no clear harmonised position in regard to dosage regimes could be achieved.

Lastly, the EBA abolished Swiss type claims as the need for these had ceased to exist in the post-EPC 2000 era. The case G2/08[56] clarifies that any further improvement in therapeutic treatments can form the basis for a patent under the EPC as long as the patentability requirements are met. Whilst the development of the further medical use patents has developed in such a way that at least on a theoretical level this is true, it remains to be seen whether this will work in practice. The answer to this depends greatly on the interpretation of G2/08 and the application of the patentability requirements to different dosage regime patents.

19 Op. Cit, Fn.6 Para. 491.
20 'Is The Enlarged Board Of Appeal Of The European Patent Office Authorised To Extend The Bounds Of Patentability? (The G3/85 Second Medical Indication/Eisai And G2/08 Dosage Regimes/Abbott Respiratory Cases)' [2011] International Review Of Intellectual Property And Competition Law.
21 Randall Lesaffer And Jan ArriëNs, European Legal History: A Cultural And Political Perspective: The Civil Law Tradition In Context (Cambridge University Press 2014) P.85.
22 Op. Cit, Fn.20.
23 William N. Eskridge, 'Interpreting Legislative Inaction' (1988) 87 Michigan Law Review.
24 For Example, Para 167: Conference Of The Contracting States To Revise The 1973 European Patent Convention (Conference Proceedings) Munich, 20 To 29 November 2000 (Mr/24/00).
25 E. Llewellyn Overholt, 'Statutes: Construction: The Legislative Silence Doctrine' (1955) 43 California Law Review.
26 G 0005/83, Eisai/Second Medical Indication, 05.12.1984; Ecli:Ep:-Ba:1984:G000583.19841205.
27 Op.Cit,Fn.20.
28 Guenther Hochhaus, Jeffrey S. Barrett And Hartmut Derendorf, 'Evolution Of Pharmacokinetics And Pharmacokinetic/Dynamic Correlations During The 20th Century' (2000) 40 The Journal Of Clinical Pharmacology.
29 Op.Cit,Fn.20.
30 T 0787/00 Kirin-Amgen, Inc. V Gruppo Lepetit S.P.A. (Ep0428267) Board Of Appeal Decision Of The Epo, 26.6.2003
31 Eddy Ventose, 'Patent Protection For Dosage Regimes In Europe: A Dissenting View' (2011) 6 Journal Of Intellectual Property Law & Practice.
32 T 0317/95, Gastrointestinal Compositions (Ep0282132) Board Of Appeal Decision Of The Epo, 26.2.1999.
33 It Must Be Noted That Comments In Regards To The Patentability Where Made In Obiter.
34 T 0004/98 Sequus Pharmaceuticals, Inc. V Inex Pharmaceuticals Corporation (Ep0496813) Decision Of The Board Of Appeal Of The Epo, 9.8.2001.
35 T 0056/97 Euro-Celtique S. A. V Takeda Chemical Industries, Ltd, Board Of Appeal Decision Of The Epo, 30.8.2001.
36 Ibid.
37 Ulrich Storz, 'Extending The Market Exclusivity Of Therapeutic Antibodies Through Dosage Patents' (2016) 8 Mabs.
38 T 0051/93,Serono Pharmazeutische Präparate Gmbh (Ep0290644) Board Of Appeal Decision Of The Epo, 8.6.1994.
39 T 0019/86,Duphar (Ep0069407) Decision Of The Board Of Appeal Of The Epo 15.10.1987 (Where A Patent Was Granted For A New Subgroup Of Patients).
40 T 0290/86 Ici Plc V Blendax (Ep0000256) Board Of Appeal Of 13.11.1990.
41 Joshua S. Gans, David H. Hsu And Scott Stern, 'The Impact Of Uncertain Intellectual Property Rights On The Market For Ideas: Evidence From Patent Grant Delays' (2008) 54 Management Science.
42 Op. Cit, Fn.14.
43 T 1020/03, Genentech, Inc, Board Of Appeal Decision Of The Epo, 29.10.2004.
44 Op. Cit, Fn.14.
45 T 0317/95, Gastrointestinal Compositions (Ep0282132) Board Of Appeal Decision Of The Epo, 26.2.1999
46 T 0056/97 Euro-Celtique S. A. V Takeda Chemical Industries, Ltd, Board Of Appeal Decision Of The Epo, 30.8.2001.
47 T 0584/97, Elan Corporation, Plc V Forschungsgesellschaft Rauchen Und Gesundheit Mbh 5.12.2001.
48 T 0485/99 Novartis Nutrition Ag, Board Of Appeal Decision Of The Epo, 29.4.2004.
49 T 0515/06 Nestec S.A., Decision Of The Epo Board Of Appeal, 18.1.2007.
50 T 0708/02 Vericore V Alpharma As And Akzo Nobel N.V., Decision Of The Epo Board Of Appeal, 4.4.2006.
51 T 1001/01 Smithkline Beecham Corporation, Board Of Appeal Decision Of The Epo, 11.10.2007.
52 T 1319/04 Kos Life Sciences, Inc., Enlarged Board Of Appeal Decision Of The Epo, 22.4.2008.
53 Op. Cit, Fn.6.
54 Op. Cit, Fn.14.
55 Op. Cit, Fn.15.
56 Op. Cit, Fn.6.

2.2. Qualitative and Quantitative Study of the patentability of Dosage Regimes at EPO level

In accordance with article 52(1) of the EPC 2000 inventions are patentable if these are “new, involve an inventive step and are susceptible of industrial application." Whether or not an invention is new is assessed based on whether or not it fulfils the requirements of Article 54 of EPC 2000. Where an invention is novel, it must then also meet the inventive step requirements outlined in Article 56. Since G2/08[57] dosage regimes are theoretically patentable, in practice, it can be seen that many dosage regimes are not patented or fail an appeal/opposition. In regard to this, it appears that the problem does not lie with the ability to prove novelty but rather in the assessment of inventive step.

This has according to this article, two main reasons. Firstly, novelty is a requirement as established above, that is much easier to meet and secondly, the EBA made the assessment and the position of the EPO much clearer in regard to the assessment of novelty rather than that of the inventive step. TBAs were therefore granted much more freedom in their assessment of the inventive step requirement, creating greater legal uncertainty. And secondly, the EBA in G2/08[58] stated, in obiter, that dosages regimes run the risk of being used abusively. This unclear and vague statement resembling the pre-G2/08 attitude of the EPO could have additionally caused more confusion and discrepancies in TBA’s interpretations to this date.

For the assessment of the inventive step requirement the EPO generally applies the problem and solution approach, which is subdivided into three steps: (1) Establishing the closest prior art. (2) Establishing the "objective technical problem" to be solved. (3) Considering whether or not the claimed invention, starting from the closest prior art and the objective technical problem, would have been obvious to the skilled person.

In order to apply the assessment of this requirement to the unclear areas of dosage regimes this empirical study aids in analysing potential features that lead to a higher chance of passing the inventive step requirement and therefore being patentable. Each step of the inventive step requirement is assessed by comparing common features in all sample cases. Features, of course, may not be viewed purely in an isolated context as they are analysed here. However, being aware of a potential factor could result in better identification of which dosage regimes have chances of being patented. This has the practical benefit that dosage regime patents applications and R&D of pharmaceuticals can be tailored towards those dosage regimes that are most likely to be successful in their application stage.

2.2.1 Method and Data Sample:

The sample Data consisted of 45 Dosage regimes cases of the EPO. The sample cases were collected with the help of the “Darts-ip” database of the private company Darts-ip, which specializes in IP case law. This database was selected as firstly, all EPO cases on Darts are obtained from the EPO itself and not through private entities[59] and secondly, Darts-ip collects decisions from all cases manually, allowing cases to be filtered through keyword searches.[60]

EPO dosage regime cases were collected based on free text keyword searches of “dosage regimes” and “dosage regime”. Cases were then selected chronologically based on their decision date; most recent cases were given priority in selection. In order for the sample cases to qualify for this study, they had to meet two requirements: (1) the cases had to enter into a discussion on the requirement of inventive step (2) the core subject of the patent had to be at least one dosage regime in accordance with the definition.

This study was found to have an estimated margin of errors equal to or smaller than +/- 12.7% and the confidence level equal to or greater than 90%. Currently, it is not possible to retrieve the actual population size of this study through the EPO, specifically PATSAT. The reason for this is that the EBA of the EPO did not provide a definition of dosage regime in its’ recent decision.[61] As a result, no clear categorization of dosage regimes is currently available upon which clear statistics of the total number of decided dosage regimes cases could be obtained. It was however possible to obtain the total number, 6031, of decisions of “second medical use” patents from PATSAT. Even though this number included second medical indication cases which are not dosage regimes, this number nevertheless served as the closest possible estimation of the population size.

2.2.2. Results

2.2.2.1. The assessment of the selection of the closest prior art

Whilst defining the closest prior art is the very first step of the inventive step requirement, it continues to be highly influential and important throughout the entire assessment. Not only does it serve as a form of benchmark of comparison against which the invention is evaluated, it also defines the formulation and therefore the scope of the technical problem.[62] Out of the 45 cases in 37 cases the closest prior was related to the same active ingredient, a feature that clearly stems from the nature of dosage regimes patents. One exception to this is where the new dosage regimes are accompanied by new medical indication. In T116/90[63], the Board of Appeal held that only prior documents with the same medical indication could constitute the closest prior art document. Hence, where a dosage regime is accompanied by a new medical indication, far fewer documents will form part of the prior art and therefore, the chance of the closest prior art being "more distant" is increased.

Dosage regime patents also face the problem and risk of the closest prior art disclosing further considerations or thoughts. This is where the prior art discloses something, which has not been tested or verified (e.g. a further research opportunity/possibility). Even though this is not a problem that most dosage regime patents face, as only 6/45 studied cases directly discussed “further considerations” of the closest prior art, where it is discussed it can be detrimental to the outcome (75% of these cases were held to not being inventive). When these 6 cases are examined closer it becomes clear that, 5/6[64] of them were found to be non-inventive on the basis of them being a "routine optimization". Where the further consideration, however, is not found in the closest prior art but in alternative prior art, EP2397189[65] indicates that this would be far less likely to lead to the finding of non-inventiveness and therefore is less threatening to the overall assessment of patentability. Furthermore, 5 out of these 6 cases concerned a new dosage rather than another type of dosage regime. It, therefore, appears that this threat of “further considerations” is largely faced by applications concerning new dosages. An applicant hoping to later receive a new dosage patent or invest in new dosage research should, therefore, be careful with the formulation of publications to ensure that vague wording of hypotheses or potential further research ideas do not hinder a later patent application for a new dosage. However, this difficulty raised by further consideration of the closest prior art could be overcome through the demonstration of obstacles to following the consideration, as was successfully done in proceedings of EP1526871[66] or by submitting evidence/prior art that could indicate that the skilled person would have not necessarily followed the closest prior art suggestion, as was successfully done in proceedings concerning the patent, EP0839039.[67]

2.2.2.2 Technical problem

When it comes to the formulation of the technical problem, formulations in the form of “an improved...” resulted in a much higher chance of being found non obvious (5/7 cases) than formulations in the form of “an alternative...”(7/14 cases). Therefore, whilst the reformulation in the form of “alternative method” does not directly mean that a patent will be held to lack an inventive step, its chances are diminished. This finding is coherent with the general position of pharmaceutical patents in general, where reformulations of problems into the “an alternative ...” resulted in cases such as T0355/97[68] and T0611/07[69] in a finding of non-inventiveness. The EPO has given the term "improvement" a wide and extensive interpretation from the applicant's point of view, resulting in the fact that any, regardless of the type or size, improvement is considered.[70] Furthermore, a wide range of factors including therapeutic properties[71], reduction of side effects[72], patient compliance[73] and duration of effect[74] are excepted.

Whilst for showing an increase in patient compliance no additional evidence is required to be submitted and therefore is therapeutic to prove. In regards to any ground other than patient compliance, the technical effect was mainly rejected because of either the fact that no evidence was submitted (42.86%)[75] or that too many variations within the comparative study exist thereby not allowing it as evidence (42,86%).[76] Hence it is essential that much care and attention should be dedicated towards submitted evidence, especially in regards to comparative studies. These should also attempt as much as possible, to establish an improved effect.

2.2.2.3 Obviousness:

In order to establish obviousness, the EPO essentially asks whether, the skilled person starting from the closest prior art, solving the problem at hand, would have arrived at the solution taking into consideration the body of prior art and the “mental furniture” of the skilled person.[77] Whilst generally, the skilled person is not permitted to "fill in" gaps of the prior art with either theoretical knowledge or his own knowledge,[78] the same is not true for dosage regime cases. In regard to new formulations, the TBA has held that the skilled person would take account of parameters relating to controlled release formulation known from the prior art and theoretical calculations known in the field of pharmacokinetics for the design of drug formulations.[79] This means that in regard to dosage regimes, the person in the skilled art has a much more active role than e.g. first medical use patents.

[57] Ibid.
[58] Ibid.
[59] This Information was supplied to me by Darts-Ip.
[60] Katrin Cremers And Others, 'Patent Litigation In Europe' (2016) 44 European Journal Of Law And Economics.
[61] Op. Cit, Fn.6.
[62] Epo Guidelines, Chapter Vii, Section 5.
[63] T 116/90 Beecham-Wuelfing Gmbh V Hoechst Ag, Board of Appeal Decision of The Epo, 03.12.199.
[64] Ibid.
[65] Brigham And Women's Hospital, Inc. V Hoffmann, Matthias Maikowski Ninnemann (Ep2397189) Decision Of The Opposition Division Of The Epo, 11.07.2017.
[66] Hexal Vs.Panion & Bf Biotech (Ep1931689), Epo, 27.07.2017.
[67] Smithkline Beecham Plc V Oragotti & Associati (Ep0839039), Opposition Division Epo, 17.11.2006.
[68] T 0355/97, Noramco, Inc V Mallinckrodt Speciality Chemicals Company (Ep289297), Board Of Appeal Decision Of The Epo, 05.07.2000.
[69] T0611/07 Evonik Stockhausen Gmbh V The Procter & Gamble Company, Nippon Shokubai Company Limited And Basf Se, (Ep1105168) Board Of Appeal Decision Of The Epo, 18.09.2009.
[70] Bengt Domeij, Pharmaceutical Patents In Europe (Kluwer Law International 2000).
[71] Hexal Vs.Panion & Bf Biotech (Ep1931689), Epo, 27.07.2017.
[72] Genzyme Corporation V Generics (Uk) Limited (Ep2664334) Opposition Division Decision Of The Epo, 26.07.2017
[73] Decision For Refusal Of Application By The Epo (Ep1931354), 30.01.2014.
[74] T964/95, The Trustees Of Columbia University/New York V Ueno Seiyaku K.K.(Ep0286903) 05.05.1999.
[75] (T 0446/13 - Bayer Consumer Care Ag V Takeda Nycomed As (28.02.2017) .
[76] (T 1374/11 Laboratorios Del Dr.Esteve S.A V Labiana Life Sciences, S.A.U (11.03.2015);, Forward Pharma V Pentafarma, Sociedade Técnico-Medicinal, Strawman And Keltie (Ep1799196) Preliminary Decision Of The BoA Of Epo, 05.02.2018) .
[77] Bardehle Pagenberg, 'Assessment Of Inventive Step Under The Epc'. (2010) .
[78] Bengt Domeij, Pharmaceutical Patents In Europe (Kluwer Law International 2000).
[79] T 0142/94 Euroceltique S.A. V Basf Aktiengesellschaft, Decision Of The Board Of Appeal Of The Epo Of 16.1.1997.

The biggest threat to the 45 cases in regard to the assessment of obviousness was routine optimization (47% of all cases that were found to not have an inventive step were held to be obvious on this ground).[80] Those cases that were not found to be obvious on the ground of routine optimization, were generally rejected because of their close proximity to the closest prior art or other prior arts used in combination. In these cases, the EPO found that either applying known pharmacokinetic knowledge to the prior art results directly in the claimed invention[81], differences between the patent and the closest prior art were small[82] or prior art documents would have led the skilled person straight to the dosage regime in question.[83] On the other hand, reasons for finding of non-obviousness included that the prior art did not provide any hint or guidance,[84] or did not outline an improved solution[85]/efficacy[86] of the new dosage regime. The scope of what can be included in routine optimization appears to be relatively broad in regard to dosage regimes cases. Cases have for example cited molar ratio[87], most effective dose[88] specific dissolution profile[89], the combination therapy from 24 to 48 weeks[90], and daily dose[91] as acts which are considered to fall within the term routine optimization. Routine optimization is of course not a new principle however its application to dosage regimes is extremely wide.[92]

New doses appear to be the form of the dosage regime that is most likely/commonly rejected due to routine optimization. More than half of all 45 studied cases that were held to be a routine optimisation were applications concerning a new dose. Dosages, therefore, appear to be at the greatest risk of being rejected on this ground rather than other types of dosage regimes such as new formulations. One reason for this is that in multiple cases, the EPO has stressed that the act of deriving a dosage is merely a routine optimization.[93] In T1409/06, for example, the TBA concluded that "the board is of the opinion that mere determination of the dosage which yields the best effect does not involve an inventive step. The skilled person is aware that the intensity of a pharmacological effect depends inter alia on the concentration of the active ingredient. This is, therefore, a matter of mere routine optimization."[94]

Statements like these appear to be, however, at least somewhat contradictory to the G02/08[95] judgment. By generalized statements dosage regimes containing only a new dose are held to not be patentable because they are outright labelled as routine optimization cases (which are not generally patentable). Most dosage regimes containing only a new dose are therefore unlikely to be granted a patent. In practice little has changed, post G2/08[96] other than the ground upon which new doses are being refused a patent on. This is also reflected in the findings of the 45 studied cases where only 6/13 dosage regimes that concerned a new dose were considered to have an inventive step. Additionally, out of these 6, 4 were with a new and another dosage regime. It, therefore, is concluded that a dosage regime, which contains only a new dose, is only patentable in exceptional cases.

2.2.2.4 Discussion and strategies for potential patentees

From a closer analysis of the application of the patentability requirements of the EPC to dosage regimes through the studied 45 cases, a number of generalized strategies can be identified. Firstly, where a patentee of a first medical indication wishes to keep the option open to later research into the field of dosage regimes, they must take much care with the wording of patent application, publications and clinical trial reports in order to avoid vague formulations that could deter a dosage regime's application. The established vague formulation of future potential research or unproven factors can still affect the assessment of inventive step. Secondly, as far as possible, patentees should strive for an "improved technical effect". These have better chances of overcoming the hurdles of the inventive step assessment.

Another strategy is the combination of different types of dosage regimes (e.g. new dose with a new mode of administration). These cases seemed to be more likely to be held[96] to have an inventive step but also appear to overcome novelty and different steps of the inventive step requirement more successfully. Out of the 45 studied cases 67% concerned more than one dosage regime were held to have an inventive step in comparison to 50% of the cases that only involved one dosage regime, and were non-obvious. The prior art for the novelty assessment and closest prior art for the inventive step test is more likely to be "less similar" to the claimed invention, thereby resulting in a technical problem that makes it more likely that it will be held as non-obvious.

Overall comparisons between the different types of dosage regimes displayed in Figure 1 below indicate that, some types of dosage regimes are generally more successful than others. Whilst new formulations appear the most likely to be patented, regimes for new doses struggle the most. The reason for this is that most of them are rejected because they are obvious in the light of closest affiliated prior art or because the dose can be obtained through routine optimization. Comparing the cases concerning new doses that were held to have an inventive step and those that were not held to have an inventive step a number of observations could be made. These could then in return be incorporated in order to make a dose-related dosage regime more likely to overcome the patentability requirements.

Firstly, cases which concern specific doses for sub-groups for which a separate dose range or regime has not yet been established appear to have higher chances in meeting the patentability requirements as was the case of patent EP2296686.[97] Secondly, new doses that focus on overcoming patient compliance appear to also be more successful as can be seen from for example the case of patent EP2265285.[98] Thirdly, new doses concerning active ingredients for which literature exists that suggests that there are particular difficulties concerning the application of pharmacokinetics to it, also have greater chances of overcoming the patentability requirements.[99] Therefore, whilst of course the chances of a new dose are not non-existent, it appears to be much more difficult to recieve such a dosage regime patent protection. Through the above-named adaptions, however, the chance of receiving a patent of the dose regime can be increased.

Comparison of the types Dosage Regime of the studied cases that were held to have an inventive step and those that did not

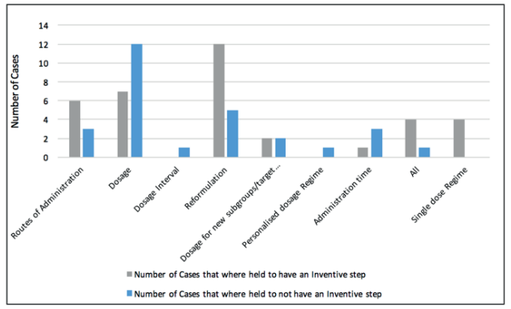

Figure 1

A dosage regime that appears to have high success rates in fulfilling the patentability requirements is a single dose regime. Out of the 4 cases that involved a single dose regime all cases were held to have an inventive step. This is firstly, because these cases are not considered to be generally derivable through routine optimization and secondly, because of their clear improvement of patient compliance that makes them automatically superior to other dose regimes. They, therefore, are likely to be held to have an "improved technical effect" without further required evidence. The EPO has accepted a general presumption that, where the administration of a drug is simplified, it will result in a greater degree in patient compliance and in return has an improved effect.[100] It is, there-fore, the factor that is the easiest to prove in order to establish an improved effect and is often not greatly affected by the prior art. Proving an improved effect due to fewer side effects or increased therapeutic effects is much harder and can involve the need for comparative experiments/evidence.

Lastly, also dosage regimes for sub-groups of patients could be seen as a strategy however it will depend greatly on whether the sub-group is new in regard to the prior art and is, therefore, a strategy which is much less predictable as the other above-named strategies. Nevertheless, it would be worth a try.

This article would, therefore, recommend that R&D is tailored towards dose regimes for single dose regimes, novel sub-groups, combining two types of dosage regimes or dosage regimes that focus on improving patient compliance as these types of dosage regimes are most likely to meet the requirements of patentability. Where however, in the process of research tailored into theses directions another dosage regime is derived, it is worth attempting to patent this.

80 See for example: T 0259/ 15, Euro-Celtique S.A., Mundipharma Laboratories Gmbh, Napp Pharmaceutical Holdings Limited, Board of Appeal Of the Epo, 25.07.2017.

81 Laboratoire Hha-Pharma and Family Health International V Generics (U.K.) Limited And Hexa/ Ag (Ep2419109) Decision Of The Opposition Division Of The Epo, 23.01.2018.

82 Decision For Refusal Of Application By The Epo (Ep1931354), 30.01.2014.

83 Gebro Pharma Gmbh V Ferring International Center S.A. (Ep1255557) Epo Board Of Appeal, 10.06.2009.

84 Appendix A, Table 33 (See Eg. Glaxosmithkline Biologicals S.A., Rixensart (Be). V Dr. Wolfgang Bock (Ep1361890), Decision Of The Opposition Division Of The Epo, 23.12.2014).

85 Akzo Nobel, Nl V Schering Ag (Ep0491415) Opposition Division Of The Epo, 24.04.2000.

86 T 0619/12, Zoetis Services Llc V Intervet International B.V., Boehringer Ingelheim Vetmedica Gmbh and Merial Limited (Ep1474067), Decision Of The Board Of Appeal Of Epo, 14.07.2017; Genzyme Corporation V Generics [Uk] Limited (Ep2664334) Opposition Division Of Epo, 26.07.2017.

87 T 0177/13, Warner Chilcott Company, Llc V Apotex Inc. (Ep1753395), Board Of Appeal Decision (11.06.2015) .

88 Hexal Vs.Panion & Bf Biotech (Ep1931689), Epo, 27.07.2017.

89 Decision To Refuse The Application By Epo(Ep2538945), 05.11.2015.

90 T 0531/04, Schering Corporation V Alfa Wassermann S.P.A., Teva Pharmaceutical Industries Ltd., Sandoz Gmbh Appelt, Christian W. Meduna And Arzneimittelfabrik Gmbh (Ep0903148) Epo, 18.11.2015.

91 Alk-Abello A/S V Merck Patent Gmbh, Mr. John Gerard Leeming And Stallergene Sa (Ep2265285), Decision Of The Opposition Division Of The Epo, 23.02.2016.

92 The Decision To Refuse The Application By EPO (Ep2538945), 05.11.2015 (In this Decision the opposition division took the approach that everything could be derived by trial and error would constitute a routine optimization).

93 Op. Cit, Fn.6.

94 T 1409/06 F.Hoffmann-La Roche Ag V Teva Pharmaceutical Industries Ltd. (Ep0689437) 1.4.2009.

95 G 0002/08 (Dosage Regime/Abbott Respiratory), Epo, 19.2.2010.

96 Ibid.

97 Gebro Pharma Gmbh V Ferring B.V. (Ep2296686), Epo, 03.01.2017.

98 Alk-Abello A/S V Merck Patent Gmbh, Mr John Gerard Leeming And Stallergene Sa (Ep2265285), Decision Of The Opposition Division Of The Epo, 23.02.2016.

99 Novartis Ag V Teva Pharmaceutical Industries Limited and Synthon Bv (Ep1556013), Opposition Division Decision Of Epo, 20.01.2012.

100 Boehringer Ingelheim Vetmedica V Intervet International Bv And Eli Lilly And Company (Ep2281829) Opposition Division Decision, Epo, 17.08.2017; Genzyme Corporation V Generics [Uk] Limited (Ep2664334) Opposition Division Decision of The Epo, 26.07.2017.

3. INFRINGEMENT OF DOSAGE REGIME PATENTS AT NATIONAL LEVEL

In Germany and the UK both direct and indirect infringement exists. Both of these infringement types must, however, "strike a balance between the two competing factors [of]" a fair protection for the patent proprietor [and] a reasonable degree of legal certainty for third parties".[101] Due to the nature of dosage regimes, many difficulties have arisen in finding the correct balance between these two factors. This is especially the case where skinny labelling is involved. In order for a pharmaceutical product to be placed on the market in Europe it must receive market authorization, something that requires information on both indications and dosages through SmPC (summary of product characteristics), PIL (patient information leaflet) and the medicinal label.[102] Even though generic products must provide the same information as their reference medicine, an exception for second medical use patent protected products exists under article 10 and 11 of Directive 2001/83/EC[103] allowing generics to exclude the patent protected use. In practice, this means that the generic products enter the market for all indications and dosage regimes except the ones which are patent protected. This act is referred to as a skinny labelling or carving out. Where then this generic product is used for dosage regimes that are not authorized for, this use is called "off-label use".

Complicating matters further, the change in claim form of dosage regime patents from Swiss type claims to EPC 2000 claims also brought with it a level of uncertainty as to the potential difference in the scope of protection of the two. Establishing whether or not a difference in the scope of protection exists is fundamental to the assessment and establishment of infringement of a dosage regime patent.

3.1. Has the scope of protection of dosage regimes changed from Swiss-type claims to EPC 2000 form claims?

When examining the preparatory works of the EPC 2000 it becomes evident that the Swiss delegation, having proposed the final version of article 54(4), had the intention of using this article to simply codify the legal position of Swiss claims. This would mean that the new EPC 2000 claims would be equivalent to that of Swiss-type claims. As EPC 2000 claims however were a replacement of the uncodified Swiss-type claims, the EBA held in G2/08 that these claims were no longer necessary and therefore, no longer allowed. In this decision, however, the EBA also held that EPC claims "are most likely broader" due to the difference in claim category. Whilst at first these findings from the EBA appear to be in contradiction to the preparatory works stated above, they are in line with earlier case law, such as Mobil[104].

This issue was further assessed in regard to article 123(3), where the TBA held that changing a claim from Swiss-type to EPC 2000 claim was a breach of Article 123(3) as this was an increase in the scope of protection of the claim. This, therefore, means that the decisions T1780/12[105] and T250/05[106], concluded that product-related claims confer a larger scope of protection than Swiss-type claims (method-related). From the perspective of the EPO, EPC 2000 claims clearly grant a wider scope of protection. Therefore, it would be expected that current infringement cases decided the on basis of Swiss-type claims may may differ from future cases regarding EPC 2000 claims.

The position of the UK courts is far less clear. Whilst on one hand Arnold, J. in Warner-Lambert Company, LLC vs Actavis Group[107] cited the case-law of the EPO concerning the increased scope of protection, which could be seen as implicitly acknowledging that a difference in protection exists,[108] a clear connection between the two claim types was also made holding that the term "for" lay central to both claim constructions. The similarities in claim construction therefore could, on the other hand, indicate that the scope of protection would not necessarily be different between the two types.[109] Nevertheless, considering that Swiss-type claims are process claims and EPC 2000 claims are product claims, this difference could indicate in itself a difference in treatment in regards to the assessment of infringement. This is enhanced by the fact that under direct infringement they would be covered by different sub-sections of section 60 of the Patents Act 1977.[110] Product claims are covered by 60(1)(a) whilst process claims are covered by 60(1)(b)-(c). As there are differences in the wordings of these subsections, infringement proceedings may differ between dosage regimes covered by EPC 2000 product claims and Swiss-type claims. Hence, also the scope of protection may be different. However, it remains to be seen how UK courts will interpret these differences, not only in regard to the claim wordings as suggested above but also in their application to the different infringement sections.

In Germany, contrary to the approach taken by the EPO, the Bundesgerichtshof (hereafter BGH) in Pemetrexed[111] has held that there is no difference in the scope of protection between Swiss-type claims and EPC 2000 claims. Both grant purpose-bound protection. The same was held in Kollagenase I[112], where the BGH held that irrespectively of the formulation, all claims which are concerned with second medical uses have as their subject-matter the specific medical use. The use is an inherent feature of the product, which the use is aimed at. According to the BGH, this correlates with the intended protection of EPC claims, making it clear that the two types of claims provide the same level of protection. Therefore, the current judgments that have been decided on the basis of Swiss-type claims.

3.2. The position in the United Kingdom

In order to understand both direct and indirect infringement in the case of dosage regimes, one must firstly understand the underlying practice of prescriptions in the UK. Generally, when a prescription is written in the UK, the doctor does not know whether the patent protected product or the active ingredient from another company is dispensed. This is because the pharmacist has the freedom to dispense either the patent protected product or a generic. When it comes to National Health Service (NHS) prescriptions, the pharmacist receives a lump sum reimbursement, which covers the price the pharmacy paid to the supplier as well as a small additional amount, a medicine margin. Therefore, the pharmacist may be motivated to dispense the cheapest generic drug in order to increase this medicine margin. However, where the prescription is not generic, the pharmacist does not have this freedom. In practice, this is nevertheless rarely the case.[113]

3.2.1. Direct infringement

As previously established, the fact that different subsections of Section 60(1) which deals with direct infringement apply to product claims and process claims, a great level of uncertainty exists in regards to legal position of infringement cases of EPC 2000 dosage regime patents. At the core of the entire section 60(1) lies however the interpretation as to what constitutes a part of a medicament. In Warner Lambert, the Court of Appeal established that a medicament is not completed at the moment of its formulation into the pharmaceutical composition[114], while it involves acts of both up- and downstream preparations. These could include for example drug packaging, labelling or patient information leaflets and providing medicaments with a wide definition for the purpose of the act.

However, in order to prove direct infringement of a Swiss-type claim by a manufacturer or supplier of a generic drug, the Court of Appeal made clear that it must be shown that these knew or could reasonably foresee the ultimate intentional use for the infringing purpose by the end user.[115] This conclusion was in the court's opinion, derived from the court's interpretation of the term "for" in Swiss-type claims. In this case, concerned with a second medical indication, the use of "Pregabalin for pain", the court concluded that where the doctor had prescribed the drug for the patented indication and the pharmacist dispensed a generic Pregabalin, knowing that it had been prescribed from the patented indication, the intentional element of the use would be met. This, however, meant that where the indication was not included in the prescription there could be no direct infringement. In practice, whilst dosage ranges and interval times are likely to be included on prescriptions, making it relatively easy to prove intent, patient group indications as well as personalised dosage regimes based on specific gene types are unlikely to be included by doctors on prescriptions making it almost impossible to prove direct infringement. The current system therefore only provides a potential protection for some types of dosage regime patents. Ironically, complicated dosage regime patents, which the UK has the greatest desirability in protecting (e.g. where a different dose is given each week or month) are for practical reasons often given to patients on separate paper rather than included on the prescription, making these the hardest to prove direct infringement for and hence enforce.

[101] Actavis Uk Ltd V Eli Lilly & Co [2017] Uksc 48; [2018] 1 All E.R. 171.
[102] Regulation (Ec) No 726/2004 On Laying Down Community Procedures For The Authorization And Supervision Of Medicinal Products For Human And Veterinary Use And Establishing A European Medicines Agency (31.03.2004). Also See Directive 2001/83/Ec On The Community Code Relating To Medicinal Products For Human Use (06.11.2001).
[103] Directive 2001/83/Ec On The Community Code Relating To Medicinal Products For Human Use (06.11.2001).
[104] G 2/88, Mobil Oil Iii V Chevron Research, Epo, 11.12.1989.
[105] T 1780/12 Board Of Regents, The University Of Texas System, Epo, 30.1.2014.
[106] T 0250/05 The Brigham And Women's Hospital, Inc. V Air Products & Chemicals Inc. And L'air Liquide S.A., Epo 4.3.2008.
[107] Warner-Lambert Company, Llc Vs Actavis Group Ptc Ehf & Others [2015] Ewhc 72 (Pat).
[108] Potter Clarkson, 'Infringement Of Second Medical Use Claims In The Uk: The Patents Court Takes With One Hand But Gives With The Other' [2015] Lexology.
[109] Paul England And Anja Lunze, 'Infringement Of Second Medical Use Patents' [2015] Lexology.
[110] Christopher Burnett, 'Swiss Claims - Full Of Holes? - A.A. Thornton & Co' (Aathornton.Com, 2015) ←Https://Www.Aathornton.Com/Swiss-Claims-Full-Of-Holes/→ Accessed 13 May 2018.
[111] BGH, Pemetrexed Grur 2016, 921.
[112] BGH, Kollagenase I Grue 2014, 464.
[113] Paul England, 'Infringement Of Second Medical Use Patents In Europe And The Unified Patent Court: Table 1.' (2016) 11 Journal Of Intellectual Property Law & Practice.
[114] Warner-Lambert Company Llc V Generics (Uk) Ltd. (T/A Mylan) & Others (2016) Ewca Civ 1006 Para. 224.
[115] Apart From Obiter Mentions In Regards To Swiss Type Claim On The Problems Of Making Intention A Relevant Issue On Infringement By Jacob J In Bristol Myers Squibb [1999] R.P.C. 253, At 271–273 The Issue Of Intent Had Not Be Considered Further By The Courts.

In the same case, Warner-Lambert[116], the Court of Appeal further held that, it would however only be foreseeable that the pharmacist would dispense the generic drug for the protected indication in the absence of other factors, making it harder to prove direct infringement of dosage regime patents. In the present case, the superintendent pharmacist had been notified that the product of the defendant was not licensed for the treatment of pain. This was done close to the date when the defendant's product had entered the market. The court held that this did, in fact, add an additional factor to the assessment and concluded that as a result, it was not foreseeable when the marketing of Pregabalin took place. This would in practice mean that simply by making a statement excluding patented dosage regimes any generic company could avoid direct infringement of the dosage regime patent. Due to the fact that the EPC 2000 claims also include the term "for use" it would be extremely likely that knowledge or foreseeability is also required mutatis mutandis in those cases regardless of the fact that the assessment would be made under Section 60(1)(a) rather than Section 60(1)(c).

Whilst no clear direction was provided in regard to the liability of doctors, the Court of Appeal indicated in Warner-Lambert that due to the current legal framework of prescriptions, it is unlikely that doctors would be liable. Furthermore, whilst the counsel for Pfizer in Warner-Lambert[117] had indicated that doctors might be liable, they held in their closing remarks that even in their opinion this was not the case. The court, in summary, held that "it is very difficult to see how a doctor could be liable for infringement of a patent merely by writing a generic prescription for Pregabalin for pain since for all doctors would know the prescription could well be fulfilled by the pharmacist by dispensing Lyrica".[118] Considering the court's reasoning there appears to be no reason that this position would be changed through the application of EPC 2000 claims.[119] In regards to pharmacists, however, it would be expected, following the same reasoning, that where they knew the dosage regime was patent protected, in other words where the dosage regime is written on the prescription, they could be potentially liable.[120] This is because they would make use of the dosage regime under either 60(1)(c) in regards to Swiss-type claims or 60(1)(a) in regards to EPC 2000 claims. No dosage regime cases have however been decided in regards to pharmacists direct liability and therefore it must be seen how courts will deal with this issue over time. As the current legal position stands in the UK, it is extremely easy for generics to escape liability through skinny labelling.

In regard to reformulations, bioequivalence can create a threat to patent enforcement. This would be the case where the formulation of the potentially infringing product is slightly different from the patent but this change is immaterial. In other words, the changes of the formulation mean that products would not fall within the literal reading of the claims but as the changes do not alter the functions of the product, it achieves the same technical effect as the patent. The recent Supreme Court decision of Actavis vs. Eli Lilly[121] has clarified this by introducing the doctrine of equivalence and made its applicability to dosage regimes clear.

The case concerned Eli Lilly's Pemetrexed compound (Pemetrexed disodium) used in combination with vitamin B12 for the treatment of cancer. Actavis's products contained Pemetrexed diacid, Pemetrexed dictromethamine, and Pemetrexed dipotassium together with vitamin B12. Reformulating the "improver questions",[122] the Supreme Court held that there was a direct infringement of Actavis's products contrary to the Court of Appeal's findings.[123] This was proceeded through the reformulation of the second question of the test, which lowered the burden of proof of the patentee. Instead of asking whether it was obvious to the person skilled in the art, it now assumes that the person skilled in the art has the knowledge. Through this reformulation of the applicable test and questions, the court has clarified two important issues. Firstly, that variants fall within the claim under normal interpretation and secondly, that they are regardless considered an "immaterial variation". However, what has been left unclear is how wide this new doctrine of equivalents is and how far it is extending. This could, therefore, have the effect that there will be a greater period of uncertainty following this case.[124] However, from the perspective of a proprietor of a dosage regime patent, especially of a new formulation, this judgment should be highly welcomed. Whilst it is clearly beneficial for dosage regimes that concern a new formulation, it is unclear whether it will have any relevance for other types of dosage regimes.

3.2.2 Indirect infringement

Indirect infringement is dealt with under section 60(2) covering situations where one, without consent of the patent owner, "supplies or offers to supply in the United Kingdom a person other than a licensee or other person entitled to work the invention with any of the means, relating to an essential element of the invention, for putting the invention into effect when he knows, or it is obvious to a reasonable person in the circumstances, that those means are suitable for putting, and are intended to put, the invention into effect in the United Kingdom." The test for article 60(2) therefore, contains a distinct knowledge requirement. It, therefore, resembles the newly introduced test under direct infringement for Swiss-type claims in part, which will most likely also be the applicable approach for EPC 2000 claims.[125] In Grimmer v Scott[126] it was established that this standard of knowledge is satisfied where at the time of supply or offer of supply the supplier knows or it is obvious in the circumstance. This knowledge requirement, however, does not contain any requirement of bad faith.[127]

Other than requiring a degree of knowledge, article 60(2) also requires that the patent must have been "put into effect". This in regard to Swiss-type claims has caused some issues and has been the reason that the courts have been relatively reluctant in the UK until recently to interpret them in a way that would be put into effect downstream. At first instance in Warner-Lambert[128] the High Court had held that indirect infringement of a Swiss-type claim could not succeed as " there can only be infringement under section 60(2) if there can be infringement by the person supplied or by a user further down the chain of supply (although it is not necessary for there actually to be an infringing act). This is not the case here since no wholesaler or pharmacist will use Lecaent to prepare a pharmaceutical composition."[129] This means in line with article 60(2), that the Swiss-type patent cannot be put into effect after the manufacturer or supplier has placed the medicine on the market.[130] However, the Court of Appeal held that it was arguable that "putting the invention into effect", may also refer joint action of a manufacturer who supplies the means to a party that than intentionally uses it for putting the invention into effect." It therefore becomes evident that the courts have generally unnecessarily melted together the "suitable for" feature of the claim with the "prepared for". This has had the effect that the courts appear to be very reluctant to grant indirect infringement to Swiss-type claims for dosage regimes or any other type of second medical use.

Compared to Swiss-type claims, the situation would appear to be more straightforward when it comes to EPC 2000 claims, this is because these are not the process of manufacture claims but particular product claims for the use in a particular therapy.[131] This means that, where a dosage regime in the EPC 2000 claim form offers to supply or supplies the product with requisite knowledge that at least some of the product in question will be used for a protected dosage regime, then infringement will arise from this. As the courts have held themselves, the vast majority, around 83% of all prescription are generic ones[132], it would therefore be foreseeable that doctors and pharmacists would prescribe and hand out a generic product for the patent protected dosage regime. This would mean that it would appear to be much easier to prove infringement of dosage regimes in the format of EPC 2000 claims than Swiss-type claims. Whether the courts will adopt this approach however, is left to be seen.

3.3. The position in Germany

The situation relating to prescription in Germany are substantially different from that in the UK, resulting in different potential infringement risks. In Germany, pharmaceutical companies and health insurers can enter into rebate agreements through §130a(8) of the German Social Law Book V. Where this is done, the pharmacist will only be reimbursed from the health insurers for a prescribed drug that they have dispensed when they must under §129(1) take these rebate agreements into account. It is through this section that the obligation to dispense that exists in Germany arises. This obligation requires the pharmacist to dispense the cheapest drug to an insured patient unless the doctor's prescription explicitly orders to provide a specific brand by striking out the "aut idem" field on the prescription form. There is however, little chance that this is done by doctors as they are motivated by budget controls to leave this field blank. In practice therefore, doctors generally allow this substitution. With regards to EPC 2000 claims the situation of infringement is much more certain in Germany than the UK, as it is clear that the current jurisprudence on Swiss-type claims will apply directly to EPC 2000 claims.

116 op. cit, fn.106.
117 Ibid.
118 Ibid. Para 686.
119 The Hon Mr Justice Colin Birss Andrew Waugh, Qc; Tom Mitcheson, Qc; Douglas Campbell, Qc; Justin Turner, Qc; Tom Hinchliffe, Qc, Terrell On The Law Of Patents (2nd Supplement) (18th Edn, Sweet & Maxwell 2018).
120 S.J.R. Bostyn, 'Personalised Medicine, Medical Indication Patents And Patent Infringement: Emergency Treatment Required' [2016] Intellectual Property Quarterly.
121 Actavis UK Limited and others v Eli Lilly and Company [2017] UKSC 48
122 Improver [1990] Fsr 181, 189.
123 It Did This By Considering Section 130(7) Of The Uk Patent Act Which Directly References To The Epc 2000. Article 69(1) Of Epc 2000 Concerning The Scope Conferred By The Claims. This Is Expanded By The Protocol, Especially Articles 1 (General Principles) And Article 2 (Equivalents).
124 Tanvi Shah Jason Raeburn And Hiroshi Sheraton, 'Actavis V Eli Lilly: English Supreme Court Shapes Up Approach To Patent Infringement By Equivalents' [2018] European Intellectual Property Review.
125 Matthew Fischer, 'Second Medical Indications And The Swiss-Form Claim: Taming Frankenstein's Monster: Part 2- Putting The Problem In Context' [2017] European Intellectual Property Review.
126 Grimme Landmaschinenfabrik Gmbh & Co Kg V Scott (2010) Ewca Civ 1110; Also See Kci Licensing In & Smith &Nephew Plc (2010) Ewca 1260.
127 Kennametal V Pramet (2015) R.P.C. 2 Ch D; Para 90 And 95.
128 op. cit, fn.106.
129 Ibid. Para 113.
130 This Finding Was In Line With The Decisions At First Instance Of The Dutch Case: Novatis Ag V Sun Pharmaceutical Industries (Europe) Bv, District Court Oft He Hague, C/09/469148/Ha Za 14-770, 25th November 2015.
131 The Hon Mr Justice Colin Birss Andrew Waugh, Qc; Tom Mitcheson, Qc; Douglas Campbell, Qc; Justin Turner, Qc; Tom Hinchliffe, Qc, Terrell On The Law Of Patents (18th Edn, Sweet & Maxwell 2018).
132 Warner-Lambert V Actavis [2015] Ewhc 72 (Pat).

3.3.1. Direct infringement

§9 of the German Patent Act states that, the patentee shall alone be entitled to use the patented invention and outlines grounds upon which one can directly infringe a patent in Germany. Claims concerning dosage regimes are, under the current law considered as "zweckgebundenes Stoffpatent" and therefore they are conferred their protection through their "Zweckbindung" purpose limitation. As clarified in "Antivirusmittel"[133] it is this purpose limitation of the dosage regime, which is inventive and therefore, it is this purpose limitation for which protection exists. Where the drug is manufactured for a different dosage regime, no infringement can take place. It is this very nature of dosage regime claims that makes infringement, especially direct, at least to some extent problematic. "Antivirusmittel"[134] therefore held that there is no infringement of a patent where the use of the patent that is protected is neither aimed at nor achieved in a targeted way.

In order to assess whether or not the use was targeted or aimed at, the courts have developed through case law[135] the concept of "sinnfällige Herrichtung", which translates into English as "manifest arrangement". In essence, this is an "objective evidence that the drug was marketed with the intention that it can be used for the indication claimed in the patent".[136] Establishing a "sinnfällige Herrichtung" requires therefore that a close link between the product as marketed and the use that is patent protected. The Düsseldorf Court of Appeal has held that this can be achieved through a number of ways such as the drug's instruction manual that includes the description of the dosage regime, the formulation of the drug, dosage or provisions of ready-to-use preparations of a drug.[137] At the same time however, the court has also made it clear that whilst those are ways to establish "sinnfällige Herrichtung", information provided about the drug in marketing materials (e.g. advertisements or flyers) or explanation from salespeople that the product can be used in a protected way do to establish a close enough link and hence do not result in a direct infringement.

This narrow scope, however, was widened through the recent judgment Östrogenblocker[138] by the Civil Court of Appeal of Düsseldorf. Manifest arrangement can according to this case still be used to establish direct infringement it is no longer the only way of establishing it. This case concerned a dosage regime patent, which was developed for a specific patient group. This patient group, however, was smaller than that, which was indicated on the packaging of the defendant's product. The defendant's product, therefore, could also be used for the patented use according to its own labelling. With closer analysis of the underlying objective of §9 of the Patent Act, it concluded that as the defendant's product was objectively suited for the patented use it would not be appropriate to not find the act infringing. The case, therefore, can be seen to not only move away from the strict approach that existed before but also as having established a new test for the assessment of direct infringement for dosage regime patents. This requires the following 2-step analysis: "(1) the product must be suited for the patented use and (2) the distributor makes use of circumstances that ensure (comparable to a manifest preparation) that the offered or distributed product is used for the protected therapeutic use. The last requirement in return requires two sub-requirements: (1) the product is amply (not only sporadically) used for the patented use and (2) that the distributor knew this, respectively shutting their eyes to this knowledge."[139] The implications of this judgment however, still remain to be seen. Nevertheless, it is clear that the scope of direct infringement has been widened especially in regard to sub-target groups.

For new doses, a link must exist between relatively easy for generics to not directly infringe the patent through ensuring that the dose is neither indicated on the label (a form of skinny labelling) and that the pills or other routes of administration do not entail the exact amount. This could easily be done where the pills contain ½ of the patented dose. No case in Germany currently exists as to whether or not a single dosage regime produced not in one pill but multiple (perhaps even only two) where the instruction gives no indication of the use is limited to a single intake, would, in fact, be a directly infringing act. Following the current case-law, however, it would most likely be concluded that this would not, in fact, be a direct infringing act as the link between the product and the single dose patent would not be close enough. It appears that, even the outcome of Östrogenblocker would most likely not affect this outcome as long as the dose of the potential infringer's products are "lower" and therefore not directly suited for the intended dose. It appears that generics could easily by-pass direct infringement of these types of patents. In regard to sub-groups, Östrogenblocker has made it clear that it is possible to find a direct infringement as long as the sub-group is also part of the original use and did not make up a too small percent of the original group. 7 % of patents falling within the patented scenario where held too small of a percentage to constitute a sufficient scope. Single digit percentage ranges are therefore unlikely to result in a finding of direct infringement. Nevertheless, where a completely new population is found these can be directly excluded from skinny labelling and hence avoid direct infringement. It would appear that these cases would be left unchanged by Östrogenblocker. However, as the established test should be seen as a case by case analysis rather than a clear-cut principle it leaves much room for future possibilities. Furthermore it was also held by District Court of Düsseldorf that not the entire process/use of the patent must be copied.[140] If a dosage regime patent consisted of two different types of dosage regimes (e.g. a new dose at a new interval) it appears that it could be sufficient if only one is directly infringed.

New routes of administration, however, as well as reformulations are much more likely to be subject to direct infringement. This is because they are more concerned with the physical state of the medicament, which cannot be easily altered. Skinny labelling, therefore, is not an option where the first indication of the drug was in oral form and the patented dosage regime is for an intravenous (IV) application. These two regimes can be seen to be much more interlinked with the actual manufacturing process. New doses, intervals and administration times, on the other hand, are quantitative and hence do not need complete customization for the use. Customisation of the drug to the use is considered by law as a preparatory act which gives rise, according to Benzolsulfonylharnstoff' to a direct infringement claim.[141] Therefore dosage regimes that require customization provide better protection against direct infringement. Furthermore, new formulations patents are also protected by the German doctrine of equivalence. The BGH held in Schneidmesser I[142] that "a variant will infringe if (i) it solves the problem underlying the invention with modified but objectively equivalent means, (ii) this would be recognised by the person skilled in the relevant art, and (iii) that person focus[sing] on the essential meaning of the technical teaching protected in the patent would regard the variant as being equivalent to the solution offered by the invention". This gives extra protection against attempts of competitors to reach the same technical effect through immaterial "designing around" the patent.

3.3.2. Indirect infringement

Indirect infringement is covered by §10(1) of the German Patent Act which states that a

> *"patent shall further have the effect that, any third party shall be prohibited, in the absence of the consent of the proprietor of the patent, from supplying or offering to supply, within the territorial scope of this Act, persons other than those entitled to exploit the patented invention with means relating to an essential element of the invention for use within the territorial scope of this Act if the third party knows or if it is obvious from the circumstances that those means are suitable and intended for using that invention."*

The BGH took a relatively wide reading of this section in Deckenheizung[143] where they held that the indirect infringement through §10 not only covers situations where the buyer uses the patented product and the supplier knows this but also situations where the buyer intends to use this patented product.[144] For the purpose of dosage regimes, this would, therefore, mean that the drug that was supplied must have been suitable as well as intended to be used for the protected dosage regime. Even though it does not require the intention to be formed at the time of supply, this appears relatively difficult to prove in regard to dosage regimes. Additionally, it remains unclear as to whether high numbers of sales would be enough to show a necessary link between knowledge of the manufacturer or supplier and the end user.

Originally German case law was so narrrow in its interpretaion of dosage regimes that skinny labelling was in fact a safe harbour both for direct as for indirect infringement.[145] However, in five parallel proceedings before the Hamburg Regional Court concerning the use of Pregabalin, it was held that, carving out and skinny labelling does not grant complete protection against indirect patent infringement. The case concerned the product of Pregabalin, which did not in its labels include the patent protected uses and indications nor did it advertise that the products could be used for these purposes. Nevertheless, the companies did enter into rebate agreements with health insurers without carving out the patent protected uses. Due to these practices and laws, the District Court of Hamburg held that infringement was a foreseeable consequence. Whilst the court did not in detail discuss the arguments of the defendants that the prescription of doctors and pharmacists could not be attributed to them, considering the backdrop of social legal frame-work outlined previously it is clear that the pharmacists and doctors had little control over the infringing acts. The substitution was carried out more or less automatically. The court additionally, quite surprisingly, stated that manifestly arrangement may not be necessary for the infringed use, but nevertheless found it was present in this case. Leaving this question of the requirement of manifestly arrangement relatively unanswered has therefore given rise to a great level of uncertainty as to the real assessment of indirect infringement.[146] On the other hand, it also opened up the possibility for more patentee-friendly decisions.

Two further judgments were decided in the same ways. The Hannover Social Court[147] and 2nd Federal Procurement Chamber[148] both granted injunctions, however only on procurement law, requiring the insurer not to enter into rebate agreements, which contradict the patent law. It therefore appears that in regard to rebates the law is relatively clear: where a dosage regime patent exists this must be carved out of a rebate agreement. The scope has been widened and clarified even further by the Düsseldorf Court of Appeal.[149] Here the court held that, even entering into a tender procedure of rebates without restrictions constitute an indirect infringement. What remains unclear is how far the case-law will develop in regard to indirect infringement. What can be concluded however, is that law of indirect infringement in Germany is moving towards a patentee-friendly system that allowed a wider scope of protection for dosage regimes.

[133] "Antivirusmittel" (Grur 1987, 794).
[134] Ibid.
[135] Originally Established In Düsseldorf District Court, "Ribavirin" 4a 0 12/03, 24 February 2004 And Then Developed Further Through.
[136] Ibid.
[137] Düsseldorf District Court, "Ribavirin" 4a 0 12/03, 24 February 2004, Grur-Rr 2004, 19. Also See: Düsseldorf Court Of Appeal, "Cistus Incanus" 2u 54/11, 31 January 2013; Düsseldorf District Court, "Chronic Hepatitis C" 4a O 145/12, 14 March 2013.
[138] Bgh, 5 May 2017 – I-2 W 6/17 – Östrogenblocker.
[139] Ibid, 9.
[140] District Court Düsseldorf Grur Rr 2001, 2004.
[141] Bgh 1977 Gewerblicher Rechtsschutzund Urheberrecht (Grur) 652 – Benzolsufonylharnstoff.
[142] Case No X Zr 168/00, 2002 Grur 519 (Schneidmesser I), Para 30; Also See Case No X Zr 156/97, 1999 Grur 977, (Räumschild).
[143] Bgh X Zr 153/03, 13 June 2006— Deckenheizung.
[144] Ibid.
[145] "Düsseldorf District Court, "Ribavirin" 4a 0 12/03, 24 February 2004, Grur-Rr 2004, 19.
[146] Lg Hamburg, 2 April 2015 Published As Grur-Rr 2015, 330 (O 24/15; 327 067/15;327 0143/15;327 0143/15;327 0132/15;327 0140/15; 327).
[147] 14 September 2015 - S 2 Kr 374/15 Er.
[148] 16 March 2015 - Vk2 - 7/15; Vprrs 2015, 0147.
[149] Court Of Appeal Düsseldorf- 1 December 2015, Az Vii-Verg 20/15.

3.4. Conclusion

In conclusion, it can be seen that in both jurisdictions, a clash exists between the regulatory laws governing the health systems and prescriptions and patent law. Dealing with this clash has been difficult for the courts, as expressed by Arnold J in Generics v Warner-Lambert. This has resulted in the fact that in the UK a much greater uncertainty remains in regard to infringement of dosage regimes. Whilst the court in Warner-Lambert clarified some issues in regards to Swiss-type claims, it created equally as many.[150] It is, for example, clear that manufacturers can avoid liability through taking reasonable steps within their power, however, it is not clear what these reasonable steps must be or more importantly whether these steps need to be considered effective. The German courts have left the area of infringement far less unclear for the patentee, however, uncertainty remains for potential infringers. It will be left to be seen how far the German courts will go with expanding the protection of dosage regimes (and other second medical uses) in cases of indirect infringement through skinny labelling. As the law currently stands, dosage regimes are more enforceable in Germany than in the UK.

Whereas direct infringement is the preferred ground in the UK for dosage regime infringement proceedings as it promises a greater success chance than indirect infringement. In Germany the opposite appears to provide more opportunities to a patentee.

There are some important legal consequences of having to rely on indirect infringement rather than indirect infringement. Firstly, indirect infringement does not cover the manufacturing but only the offer or sale in Germany. Therefore, where a dosage regime is produced in Germany but sold outside of Germany, direct infringement would not protect the patentee against this. Secondly, in regard to indirect infringement, the damages can only be rewarded in regards to the extent to which the patentee could prove that the contested product was actually used for the claimed product. This in practice could be relatively hard especially with dosage regimes patents.

A desirable international shift towards greater consistency can however, also be observed through recent case law developments such as Actavis UK Ltd v Eli Lilly & Co[151]. The Supreme Court highlighted this in Schütz (UK) Ltd v Werit (UK) Ltd[152] stating that "complete consistency of approach" between different national courts of the EPC states "is not a feasible or realistic possibility at the moment", but nonetheless "it is sensible for national courts at least to learn from each other and to seek to move towards, rather than away from, each other's approaches". Therefore, it is clear that differences between the member states will remain, however a general trend towards greater harmonization can be observed. In regard to dosage regimes, this appears to mean that the UK is more willing to follow the more patentee-friendly approach of Germany. This should be greatly welcomed by the patentee or potential patentee of a dosage regime.

3.4.1. Suggestions to potential and current patentees of dosage regimes

Additionally, as it appears that sub-target groups and therefore, also sub-doses are easiest to bring infringement proceedings against in both Germany and the UK potential patentees are encouraged to direct their research into this field as to at least include this type of dosage regime within their patent claims. Due to the doctrine of equivalence in both systems infringement of new formulations also has a greater level of protection. On the other hand, administration time and interval regimes are the easiest for generic companies to avoid infringement proceedings in and therefore give the weakest protection. Where these are in combination with another regime, the success chances of an infringement proceeding are drastically increased. In conclusion, it should also be noted that as both the German and UK systems are moving towards greater patent protection, until the boundaries of the current laws are clearly defined, it may be worth attempting proceedings in the hope that the court continues on down this road of increased protection for patentees.

3.4.2. Suggestions for generics

In Germany, it would hence be suggested for generic companies to avoid entering into rebates or tenders and tender agreements unless all patented dosage regimes have been explicitly carved out and excluded. Health insurances are additionally advised to check the overlap of regulatory laws and patent law, as a clash will not guarantee protection against the latter. In the UK generics are advised to make an explicit announcement to pharmacies at the time of marketing that their drug is not suited for the patent protected dosage regimes. This act appears, as case law has shown to be sufficient to avoid infringement. As the position in regard to indirect infringement as to EPC 2000 claims is highly unclear, generics are advised to be careful in regards to skinny labelling, as a greater degree of desired harmonisation can be seen between the UK and Germany. Therefore, the UK may therefore follow the more patentee friendly approach of Germany in regard to indirect infringement.

[150] Matthew Fischer, 'Second Medical Indications And The Swiss-Form Claim: Taming Frankenstein's Monster - Part 3: The Franken-Cuckoo Comes Home To Roost' [2017] European Intellectual Property Review.

[151] op. cit, fn.101.

[152] Schütz (Uk) Ltd V Werit (Uk) Ltd (Nos 1 To 3) [2013] Bus Lr 565; [2013] Rpc 16 Para. 40.

[153] Agreement On The Unified Patent Court (Signed 19th Feburary 2013) (Upc) And Regulation (Eu) No 1257/2012 Of The European Parliament And Of The Council Of 17 December 2012 Implementing Enhanced Cooperation In The Area Of The Creation Of Unitary Patent Protection.

[154] 24(1)(E) In Full Compliance With Article 20, When Hearing A Case Brought Before It Under This Agreement, The Court Shall Base Its Decisions On National Law.

[155] 'Can You Protect Dosage Regimes In France? | Lexology' (Lexology.Com, 2018) <Https://Www.Lexology.Com/Library/Detail.Aspx?G=170e087c-E19d-4830-9ae8-A4ee-d5a78486> Accessed 11 May 2018.

4. FINAL REMARKS

Whilst theoretically dosage regimes are patentable under the EPC 2000, in practice, these patents appear to struggle in meeting the requirements under the convention. Many dosage regimes are therefore left unprotected. The problem, however, does not lie in overcoming the hurdle of novelty but in fact meeting the requirements of the inventive step requirement. Not only does the problem and solution approach, due to its strong focus on the closest prior art and problem reformulation, appear to not be the most appropriate approach for dosage regimes, the decisions within the EPO are also inconsistent. After a difficult and perhaps lengthy struggle at EPO level, dosage regimes continue to face problems at national level. Despite overlaps and the court's attention to further harmonization, the current legal position between Germany and the UK differs greatly. The abolishment of Swiss-type claims and the introduction of EPC 2000 claims added additional fuel into the fire. Not only is the scope of protection of these latter claim formats in regard to dosage regimes unclear but also different. In the UK this has additionally resulted in the fact that infringement proceedings and therefore patent enforceability is left completely unclear and unpredictable. This is highly detrimental to both current and potential patentees and competitors. Therefore, closing one door of uncertainty in G2/08 opened others.

Whilst a trend can be observed towards decreasing the hurdles that dosage regimes must overcome in order to be rewarded and retain a patent, the law remains highly unclear. It appears that whilst in theory dosage regimes are patentable, the position in practice has not changed drastically. Whilst before dosage regimes were being rejected on the basis of industrial application or method of treatment exclusions, they are now being rejected on the ground of lacking an inventive step as they are routine optimizations. This appears to be the case as a general presumption amongst the EPO and the UK courts that developing the dose of any drug is a simple routine optimization task, which is generally carried out. This approach, however, takes all the work and knowledge required to develop a dosage regime for granted, in inadequately rewarding the work and effort required.

Legal uncertainty is highly undesirable from the prospect of a patentee. However, this article has established strategies based on trends in current case law that may allow greater chances in the patentability of dosage regimes and tailoring of R&D budget allocations. In conclusion, therefore, patent applications should as far as possible be filed encompassing multiple dosage regimes (e.g. new dose and new route of administration). Furthermore, new formulations and single dose regimes should currently receive a high level of focus due to their greater chances of being patentable. As regimes for a new dose have relatively low chances of being patented, these should be focussed on improving patient compliance, concern a specific subgroup or be designed for drugs for which a particular difficulty exists. Additionally, sub-target and dose groups, as well as new formulations, are likely to receive better patent protection.

The clear lack of certainty requires, more adequate and detailed guidelines for assessment for the EPO. A greater need for consistency, clarity and transparency can be obtained by establishing clearer guiding principles in regard to how the inventive step requirement is to be assessed for dosage regimes. Additionally, patent law therefore should attempt as much as possible to seek a balance between the different stages of research: drug discovery and drug development. Adequately rewarding of both is the suggestion of this article. This would entail increasing the protection and enforcement of dosage regime patents and ensuring that first medical use patents are only granted protection for properties that are known at the time of filing. Ensuring such a balance is achieved would furthermore be in line with the social contract theory. Lastly, this article suggests revisiting the regulatory laws that appear in conflict with the patent law. The answer does not necessarily have to lie within the field of patent law.

The differences in invalidity and infringement proceedings between the UK and Germany signal potential difficulties in finding a common ground for the Unified Patent Court system. This is enhanced by the fact that, whilst prescription practices differed between Germany and the UK, in both cases the national laws of these interacts with the laws of patent law. Article 25 and 26 concerning infringement of the agreement on the Unified Patent Court[153], must according to Article 24(1)(e)[154] be read in line with national law. This article would, therefore, urge further research into this area in order to develop an appropriate starting point for the Unified Patent Court in regard to dosage regimes and appropriate methods of how this system will overcome the challenges caused by the quickly evolving law of dosage regimes at national level. In line with this suggestion, this article further calls for further research into different jurisdictions not covered by the article. One example of this would be France, where much uncertainty remains in regard to the exclusion from patentability of dosage regime claims.[155]

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Safeguarding public health in the wake of hegemonic intellectual property rights – Two means to this end?

By Katarina Foss-Solbrekk

1. INTRODUCTION

In a world with an estimated population of 7.6 billion, 2 billion people lack access to medicines that are imperative to their health and survival.[1] Consequently, 15,000 deaths per day (more than half of the 5.6 million children who died before their fifth birthday in 2016) could have been prevented with the provision of essential health services.[2] In total, the World Health Organisation (WHO) estimates that at least 18 million people die needlessly each year from medicinal inaccessibility.[3] The geographical distribution of those unable to access medicines is concentrated in developing countries (DC) and least developed countries (LDCs). As a result, the same disease with a 90% cure rate in America can have a 90% death rate in Africa.[4]

While there are many conclusions that one may draw from these figures, one thing is clear: the inability to access medicines in DCs and LDCs remains a pressing global problem, and one that prevails despite the safeguards present under international law. International human rights law protects the right to health, including access to medicine. Additionally, international intellectual property (IP) law permits compulsory licenses (CLs), offering countries a means to circumvent intellectual property rights (IPRs) to preserve public health, given that the unaffordability of medicines is attributed mainly to patent rights. While it is true that patent rights do not solely inhibit medical accessibility (socio-economic and political factors also play a role) it is also true that patent rights granted under the multilateral legal agreement on 'Trade-Related Aspects of Intellectual Property Rights' (TRIPS)[5] allow pharmaceutical companies to inflate prices well above marginal costs, thereby undermining the right to health.

A CL constitutes a legal measure which, in theory, may be used to effectively fulfil obligations under the right to health. However, historically, external variables such as retaliation from foreign States and pharmaceutical companies, as well as legislative difficulties, have suppressed CL usage. Despite the Doha Declarations[6] reassurance of countries' right to use CLs to uphold public health duties, as well as the adoption of Article 31bis (enabling countries to import medicines under a license) the effective use of CLs remains caught in a web of issues. These issues are in turn exacerbated by the proliferation of bilateral and multilateral free trade agreements (FTAs) with IP provisions surpassing TRIPS requirements. Consequently, the feasibility of using CLs is limited in several countries.

In a turn of events, these issues have led to the increased issuance of voluntary licenses (VLs), whereby countries use the threat of imposing CLs to obtain VLs from pharmaceutical firms. The emergence of VLs has, furthermore, led to the nascence of the Medicines Patent Pool (MPP) - an entity dedicated to brokering VLs for pharmaceuticals in DCs and LDCs. While VLs can act as a countervailing force against certain of the issues arising from CLs, VLs can themselves entail certain issues impeding accessibility to medicine. In light of these developments, a re-evaluation of how CLs and VLs are used to safeguard public health is necessary.

In this paper, the new private ordering of CLs and FTAs, as well as VLs, are explored. It is argued that countries and pharmaceutical firms now seek to limit the use of CLs through FTAs and investor-state arbitration proceedings. Additionally, it is shown that CLs may be used to strike VLs. While VLs improve medical accessibility and escape the procedural difficulties and resistance obstructing CLs, their focus on HIV/AIDS drugs and geographical exclusions limits its reach. Thus, this paper demonstrates that CLs and VLs should be used as complimentary regimes as, independently, each licensing scheme falls short of comprehensively improving access to medicines and protecting the right to health.

2. INTERNATIONAL LEGAL FRAMEWORK: INTELLECTUAL PROPERTY RIGHTS & THE RIGHT TO HEALTH

2.1 IP, human rights and access to medicines

We will begin with an outline of the background behind CLs, as well as an outline of the relationship between international IP law and the right to health. The right to health is a universal human right, at least 115 national constitutions.[7] As well as being secured and advanced through international and national human rights law, treaties, and United Nations (UN) resolutions and declarations, this right is protected under Article 25 of the Universal Declaration of Human Rights.[8] Although the Declaration has no binding effect, as it is not a treaty and thus does not impose obligations on signatories directly, it remains an authoritative framework.[9] All WTO Members have ratified at least one international human rights instrument protecting the right to health.[10]

One of the most influential human rights instruments is the International Covenant on Economic, Social and Cultural Rights (ICESCR).[11] Article 12 of the ICESCR stipulates that the right to health entails "the right of everyone to the enjoyment of the highest attainable standard of physical and mental health," including "the creation of conditions which would assure to all medical service and medical attention in the event of sickness."[12] The ICESCR is an international treaty that has been ratified by at least 85% of WTO members who are therefore bound by its terms under the principle of *pacta sunt servanda*.[13] Under this principle - states must comply with the terms of any international agreement they adopt - states who sign treaties containing provisions regarding the right to health are legally bound to uphold this right.[14] Additionally, human rights treaties are not subject to the principle of in dubio mitius, that is, interpreting treaties restrictively to preserve state sovereignty. Instead, human rights treaties are interpreted to afford "effective protection" of the rights conferred.[15]

The extent of which the right to health imposes an obligation on States differs depending on the source. On an international level, however, it is widely acknowledged that, given the legal force of the ICESCR, the ad minimum core obligation of the right to health entails access to essential medicines.[16] Thus, the right to health imposes a positive obligation on States to progressively respect, protect and fulfil this right,[17] by which access to essential medicines is recognised as, "one of the fundamental elements in achieving progressively the full realisation" of the right to health.[18]

According to the Committee to the ICESCR, access to medicines comprises four main elements: quality, acceptability, availability and accessibility - that is economic and physical accessibility.[19] Put simply, it includes a duty "to prevent unreasonably high costs for access to essential medicines."[20] It is worth noting that the Committee links essential medicines to those included on the WHO compiled essential recommended medicines list.[21]

The Committee, furthermore, has confirmed that State practice which infringes Article 12 of the ICESCR includes the adoption of laws and policies interfering with any component of the right to health, and failure to consider the State's legal obligations surrounding the right when agreeing to "bilateral or multilateral agreements with other States, international organisations and other entities, such as multinational corporations."[22] Foreign States, too, have an extraterritorial obligation to not influence other States in such a way as to hinder that State from complying with ICESCR obligations, such as when negotiating trade agreements.[23] General Comments are not binding, but they are authoritative and instructive as to the object and purpose of the ICESCR.[24]

1 World Health Organization, "Access to Medicine Index 2018 – Methodology Report," 6.
2 UNICEF & United Nations Inter-Agency Group for Child Mortality Estimation, "Child Mortality Estimates: Global and Regional Under-Five, Infant and Neonatal Mortality Rates and Deaths" 19th October 2017.
3 Statistics obtained from documentary "Fire in the Blood" directed by Dylan Mohan Grey, released on the 12st of February 2013; Devi Sridhar, "Improving Access to Essential Medicines: How Health Concerns can be Prioritised in the Global Governance System," Public Health Ethics 1, no. 2, (2008): 83.
4 Donald G. McNeil Jr, "As Cancer Tears Through Africa, Drug Makers Draw Up Battle Plan," The New York Times, 7th October 2017.
5 Agreement on Trade-Related Aspects of Intellectual Property Rights, 15th April 1994, Marrakesh Agreement Establishing the WTO, Annex 1C, Legal Instruments – Results of the Uruguay Round, 33 I.L.M 1197 (1994) (hereinafter 'TRIPS').
6 WTO, Ministerial Declaration of 20th November 2001, WT/MIN(01)/DEC/2, 41 I.L.M 755 (2002) (hereinafter 'the Doha Declaration').
7 Final Report of the UN Secretary-General's High-Level Panel on Access to Medicines, September 2016, 16.
8 UN General Assembly, "Transforming our World: The 2030 Agenda for Sustainable Development," A/RES/70/1, 25th September 2015; UN Human Rights Council, A/HRC/RES/32/15, 18th July 2016; UN Human Rights Council, "The Right of Everyone to the Enjoyment of the Highest Attainable Standard of Physical and Mental Health in the Implementation of the 2030 Agenda for Sustainable Development," A/HRC/35/L.18/Rev.1, 21st June 2017.
9 Frantzeska Papadopoulou, "TRIPS and Human Rights" in Intellectual Property Rights in a Fair World Trade System: Proposals For Reform of TRIPS, ed. Annette Kur and Marianne Levin (Cheltenham: Edward Elgar Publishing, 2011): 261-262.
10 Papadopoulou, "TRIPS and Human Rights," 271.
11 International Covenant on Economic, Social and Cultural Rights, GA Res. 2200A (XXI), 21 UN GAOR Supp. (No.16) at 49, UN Doc. A/6316 (1966); 993 UNTS 3; 6 I.L.M 368 (1967) (hereinafter 'ICESCR).
12 Article 12(2)(d) of ICESCR.
13 Article 18 of the Vienna Convention on the Law of Treaties, 115 U.N.T.S. 331, 8 I.L.M, 679, 23rd of May 1969, (hereinafter 'VCLT'); Holger Hestermeyer, Human Rights and the WTO: The Case of Patents and Access to Medicines, (Oxford: Oxford University Press, 2007): 102; Frédéric Mégret, "Nature of Obligations," in International Human Rights Law ed. Daniel Moeckli et al., (Oxford: Oxford University Press, 2010): 98.
14 Christine Chinkin, "Sources," in International Human Rights Law ed. Daniel Moeckli et al., (Oxford: Oxford University Press, 2010): 79.
15 Hestermeyer, Human Rights, 86.
16 Hestermeyer, Human Rights, 136.
17 Article 2 and 12(1) of ICESCR; A Eide, The New International Economic Order and the Promotion of Human Rights, Report on the Right to Adequate Food as a Human Right, UN Doc E/CN.4/Sub.2/198723 (1987) paras 66.
18 UN Human Rights Council, "Promotion and Protection of All Human Rights, Civil, Political, Economic, Social and Cultural Rights, Including the Right to Development," A/HRC/RES/12/24, 12th October 2009.
19 Committee on ICESCR, "The Right of Everyone to Benefit from the Protection of the Moral and Material Interests Resulting from any Scientific, Literary or Artistic Production of Which He or She is the Author," Article 15, para 1(c), General Comment No. 14 (2005), E/C.12/GC/1, 12th January 2006, para 35 (hereinafter 'the Committee'); Stephen P. Marks, "Access to Essential Medicines as a Component of the Right to Health," in Realizing the Right to Health, ed. Andrew Clapham and Mary Robinson (Zurich: Rüfer and Rub, 2009): 82.
20 Ibid.
21 Sarah Joseph, Blame it on the WTO?: A Human Rights Critique (Oxford: Oxford University Press, 2011): 218.
22 Committee on ICESCR, General Comment No. 14, para 50.
23 Committee on ICESCR, "State Obligations under the ICESCR in the Context of Business Activities" General Comment No. 24, E/C.12/GC/24, 10th August 2017, para 28-29.
24 Nisuke Ando, "General Comments/Recommendations" in The Max Planck Encyclopedia of Public International Law ed. Rüdiger Wolfrum (Oxford: Oxford University Press, 2008).

International and national courts also apply and adjudicate on the right to health. The International Court of Justice in its Advisory Opinion in the *Legal Consequences of the Construction of a Wall* cemented the justiciability and legal force of the right to health, along with other rights included under the ICESCR, by confirming the ICESCR's applicability and relevance when evaluating the legality of Israel building a wall in occupied Palestinian territory.[25] Furthermore, several national courts recognise that medicinal access forms part of the right to health.[26] In *Cruz Bermúdez*, the Venezuelan Supreme Tribunal ascertained that the government was obligated to provide HIV/AIDS treatments to *all* patients, as the right to health and the right to access to medicines is protected under the Venezuelan Constitution.[27] Similarly, in *Treatment Action Campaign*, the South African Constitutional Court instructed the State to better provide access to a specific HIV drug due to the government's health duties.[28]

In *Patricia Asero Ochieng*, the Kenyan High Court went one step further and found that the right to health may take precedence over a patent holder's IPRs.[29] In this case, several HIV/AIDS patients claimed a Kenyan law, which failed to distinguish between counterfeit goods and generic medicines, threatened their ability to access essential medicines and violated their right to health.[30] In its reasoning, the court *inter alia* applied the right to health under the Kenyan Constitution, as well as the ICESCR, and affirmed that the State has both a positive obligation towards its citizens to enable medical access and a negative obligation to refrain from acting in a manner that impedes these health services.[31] Although these cases are not binding on an international level, they are persuasive in their elucidation of State practice. Moreover, these cases demonstrate how national courts balance IPRs and the right to health, where the latter is used as justification to enable medical access.

Yet, steep prices on medicines remain a barrier to accessibility and to the fulfilment of the right to health in DCs and LDCs. It is therefore claimed that high medical prices infringe the right to health.[32] A counterclaim to this is that, although States have an obligation to ensure that medicines are accessible and affordable, they must not set prices. Under the inventor's 'monopoly' patent rights, this is their prerogative. It is this point that gives CLs their relevance. CLs allow governments to increase affordability, forming part of a State's obligations under the right to health. Due to these obligations, and CLs role in fulfilling them, States have a responsibility "to do all they reasonably can to make sure that existing medicines are available," including, "using CLs", as reaffirmed by the UN Special Rapporteur.[33]

It is worth noting that the ICESCR and other treaties solely impose public health obligations on States, not on the non-State actors who set pharmaceutical prices.[34] However, a 'social contract' between the inventor and society is embedded in patent law: in exchange for sharing their inventions, inventors are entitled to certain exclusive rights. This is aimed at encouraging future innovation, which in turn benefits society.[35] Despite this social contract, as will be shown, inventors fail to conduct R&D for diseases afflicting DCs and LDCs, price drugs well out-of-reach for these citizens and oppose licenses due to their financial interests, thereby failing to 'share' their inventions. Thus, there is a similar normative justification for enabling medicinal access through licensing to be made against inventors.

Notwithstanding this background, medical inaccessibility remains a pressing problem in DCs and LDCs, whereby the right to health is not equally enjoyed around the world. This not only reveals the stark contrast between how the right to health exists on a theoretical level and how it is employed in practice, but also how certain rights protected as human rights and as IPRs may conflict. As patents allow inventors to set prices above marginal costs, IPRs affect the right to health directly.[36] Therefore, to remedy this conflict, the international IP framework permit CLs.

25 Legal Consequences of the Construction of a Wall in the Occupied Palestinian Territory, Advisory Opinion International Court of Justice Report 136, 9th July 2004, paras 113, 130.

26 Social and Economic Rights Action Centre and the Centre for Economic and Social Rights v Nigeria, Communication No 155/1996, ACHPR/COMM/A044/1, 27th May 2002, para 53f.

27 Cruz Bermúdez v Ministerio de Sanidad y Asistencia Social, Tribunal Supremo de Justicia de Venezuela, Case no 15.789, Decision No 916 (1999); Hestermeyer, Human Rights, 104.

28 Minister of Health v Treatment Action Campaign (2002) ZACC 15; 2002 (5) SA 721; 2002 (10) BCLR 1033.

29 P.A. Ochieng, M. Atieno and J. Munyo v Attorney General, Petition no. 409 of 2009, Judgment of the Kenyan High Court, April 20th 2012; Emmanuel K. Oke, "Incorporating a Right to Health Perspective into the Resolution of Patent Law Disputes," Health and Human Rights 15, no. 2 (2013): 103.

30 Ibid, paras 1, 14.

31 Ibid, para 66.

32 Hestermeyer, Human Rights, 78.

33 UNGA, "Report of the Special Rapporteur on the Right of Everyone to the Enjoyment of the Highest Standard of Physical and Mental Health, Paul Hunt," UN Doc. A/61/338 (13 September 2006) para 47.

34 Article 2 of ICESCR.

35 Susy Frankel and Jessica C. Lai, "Recognised and Appropriate Grounds for Compulsory Licences: Reclaiming Patent Law's Social Contract," in Compulsory Licensing: Practical Experiences and Ways Forward, ed. Reto M. Hilty and Kung-Chung Liu (Heidelberg: Springer, 2014): 150, 159, 161.

36 Oke, "Incorporating a Right to Health," 98.

2.2. Safeguarding of public health: Compulsory Licenses

The Paris Convention for the Protection of Industrial Property introduced CLs into international law.[37] Article 5 allows for CLs to prevent abuses that may arise from exclusive patent rights or when the right holder fails to work the patent, otherwise known as 'the local working requirement.'[38] The Paris Convention remains in force,[39] though TRIPS incorporated Articles 1 to 12 of the Paris Convention upon its ratification in 1995.[40] TRIPS regulates IPRs between WTO members and, in short, sets the ad *minimum* quasi-universal IP protection standards and enforcement measures members must abide by.[41]

The object and purpose of TRIPS under Articles 7 and 8 elucidates how TRIPS seeks to strike a balance between IPRs and public health. Article 7, inter alia, provides that the protection and enforcement of IPRs should "contribute to the promotion of technological innovation and transfer and dissemination of technology," and occur "in a manner conducive to social and economic welfare, and to a balance of rights and obligation." Article 8(1), inter alia, affirms that Members may, "adopt measures necessary to protect public health and nutrition, and to promote the public interest in sectors of vital importance to their socio-economic and technological development."

Although neither Article mentions the right to health per se, the wording of the Articles arguably lay the basis of the understanding that TRIPS is to be interpreted in a manner allowing Members to uphold their public health obligations. These Articles therefore represent an 'opening' where the right to access medicines may be used as an argument to interpret Article 31 liberally.[42] Article 31 permits "other use of the subject matter of a patent without the authorisation of the right holder, including use by the government or third parties authorised by the government." In other words, Article 31 allows for CLs - a non-voluntary arrangement that allows parties to circumvent patent rights to authorise "domestic entities (public or private) to import, produce, and distribute patented goods."[43] CLs lead to the decrease of drug prices in that other parties, with production costs nearing zero per-unit level, may enter the market.[44] By solely incurring these production costs, without astronomical R&D expenditures, such astronomical expenditures are not passed on to the consumer.[45]

Article 31 also enumerates a list of preliminary conditions a party must fulfil to issue a CL. To grant a license, a State must: provide adequate remuneration to the respective right holder; attempt to negotiate a VL with the right holder prior to issuing a CL – this criterion extinguishes in the event of "a national emergency or other circumstance of extreme urgency;" use the patent solely for the purpose of its authorisation; authorise the CL "predominantly for the supply of the domestic market;" construct the CL to be non-exclusive and subject it to judicial review.[46] All CLs must also be assessed by the country on a case-by-case basis and configured according to the situation at hand and the purpose for which it was authorised.[47] While it is worth noting that these conditions are not obligatory if the license is to remedy anti-competitive practices,[48] this article focuses primarily on those grounds for CLs in which the conditions apply.

37 The Paris Convention for the Protection of Industrial Property, 20th March 1883, as revised at the Stockholm Revision Conference, 14th July 1967, 21 U.S.T. 1583, T.I.A.S. No. 6903, 828 U.N.T.S 305 (hereinafter 'the Paris Convention').

38 Ibid, Article 5(1)-(4).

39 Paul Champ and Amir Attaran, "Patent Rights and Local Working Under the WTO TRIPS Agreement: An analysis of the U.S. Brazil-Patent Dispute," Yale Journal of International Law 27 (2002): 372.

40 Article 2(1) of TRIPS.

41 Frederick M. Abbott, "The Enduring Enigma of TRIPS: A Challenge for the World Economic System," Journal of International Economic Law (1998): 499.

42 The Panel Report in Canada-Pharmaceutical Patents, WT/DS114/4, 7th April 2000, paras 7.24-7.26 stated that Articles 7 and 8 must be "borne in mind" when interpreting other TRIPS provisions.

43 Kenneth C. Shadlen, et al., "Globalization, Intellectual Property Rights, and Pharmaceuticals: Meeting the Challenges to Addressing Health Gaps in the New International Environment" in Intellectual Property, Pharmaceuticals and Public Health: Access to Drugs in Developing Countries (Cheltenham: Edward Elgar Publishing, 2011): 17.

44 Charles R. McManis and Jorge L. Contreas, "Compulsory Licensing of Intellectual Property: A Viable Policy Lever for Promoting Access to Critical Technologies?" in TRIPS and Developing Countries: Towards a New IP World Order? ed. Gustavo Ghidini, Rudolh J.R. Peritz and Marco Ricolfi (Cheltenham: Edward Elgar Publishing, 2014): 125.

45 Maura Nuno, "A Fair Return Approach to Pharmaceutical Compulsory," Case Western Reserve Journal of International Law 48, no. 1 (2016): 404.

46 See Article 31(a)-(k) of TRIPS for full list of requirements.

47 Articles 31(a)-(c) of TRIPS; Jerome H. Reichman, "Comment: Compulsory Licensing of Patented Pharmaceutical Inventions: Evaluating the Options" Journal of Law, Medicine & Ethics 23, (2009): 252.

48 Article 31(k) of TRIPS.

In sum, CLs constitute a measure States may employ to safeguard public health. However, after TRIPS took effect in 1995, Article 31 only ostensibly protected public health, while the robust IP standards otherwise imposed by TRIPS nevertheless threatened to thwart access to affordable medicines.[49] Despite the existence of CLs, countries with little or no local manufacturing capabilities were unable produce drugs locally and at the same time prohibited from importing medicines under a license pursuant to Article 31(f). For countries able to produce drugs, the prices offered under a CL were still not affordable.[50] This issue escalated in the wake of the HIV/AIDS epidemic in the late 1990s. During this time, the right to health appeared precarious as IPRs prevailed over individuals' inability to access affordable drugs. This dire situation prompted another round of multilateral trade negotiations, resulting in the Doha Declaration in 2001. The Doha Declaration achieved two pertinent objectives.[51] First of all, it clarified that TRIPS is to be interpreted in light of the obligations surrounding the right to health. To this end, it reaffirmed Members' right to utilise TRIPS flexibilities to circumvent IPRs for improving access to medicines.[52] This is embedded in Paragraph 4 of the Declaration, which states that TRIPS,

> *"can and should be interpreted and implemented in a manner supportive of WTO Member's right to protect public health, and, in particular, to promote access to medicines for all."*

Second, it made an overture for greater medicinal access by instructing the TRIPS Council to resolve the issue of CLs and LDCs with little or no manufacturing capabilities.[53] On this point, the Council reached a decision on the 30th of August 2003, establishing that LDCs and other countries lacking manufacturing capacities may import drugs under a CL.[54] The Council incorporated this 'Waiver Decision' into TRIPS as amendment 'Article 31bis' in January of 2017.[55] However, the Doha Declaration only *prima facie* resolved the issues with CLs. Issues remained with Article 31bis and, as the Declaration failed to mediate the tensions that had been stirring between WTO Members since negotiating TRIPS, these tensions continued to dissuade the use of CLs.[56] Thus, the procedural and political difficulties of employing CLs survived into the post-Doha era, only now inhibiting both Articles 31 and 31*bis*,[57] including the further requirements contained in the latter.

One example of these difficulties can be seen in the requirement for the importing country to notify the TRIPS Council of its intent to issue a CL, specifying the product name, the quantities to be imported, the measures taken to prevent re-export.[58] The exporting country must inform the Council of its intent to grant a CL, specifying the product, export quantities and the final destination, and with the products displaying distinct features signalling that they are produced under the CL.[59] Additionally, all information must be published and publicly available online.[60] Notwithstanding these requirements, the grounds for issuing CLs remain at the discretion of States themselves and primarily a matter of national law.

2.3. Also a matter of national law

Paragraph 5(b) of the Doha Declaration manifests that each member retains "the freedom to determine the grounds upon which such licenses are granted," provided that he Article 31 requirements are adhered to. As Article 31 and 31bis are not self-executing for all countries - these countries must enact ancillary legislation to implement CL provisions in their respective jurisdictions. This gives countries leeway to determine autonomously the scope of the procedural conditions and the grounds for issuances, which differ from state to state as a result.[61]

How grounds to issue CLs vary between states is confirmed in a study of 41 DCs. Its results reveal that: 39 countries include failure to exploit a patent to meet public demand after 3-4; 33 countries allow for public non-commercial use; 29 countries permit dependent patents; 24 countries to remedy anti-competitive practices; 22 countries mention national security, healthy emergencies or to develop a vital economic sector, and 2 countries provide no specific provisions.[62] Hence, these findings reveal how the basis for granting a CL varies depending on national laws.

Grounds also vary due to bilateral and multilateral FTAs signed between States. As a result of these agreements, the grounds for which some countries may issue CLs are restricted and countries expected to use TRIPS flexibilities adopted stronger IP standards prior to the TRIPS deadline.[63] This is discussed in further detail in section 3.1. In 2013, the TRIPS Council, pursuant to Article 66.1, extended the transition period deadline for LDCs to implement the TRIPS minimum standards to July of 2021.[64] As of now, only 20 African countries are among the 87 countries to have ratified Article 31*bis*, despite the continent containing the greatest number of LDCs.[65] This may be one of several reasons for why Article 31bis, thus far, has not been employed as extensively as envisaged. Meanwhile, use under Article 31 appears more prevalent than putatively reported.[66]

3. COMPULSORY LICENSES: HISTORIC USES AND CONTEMPORARY CHALLENGES

3.1 Background

To date, it is reported that the governments of 24 countries have granted at least 34 CL requests from third parties to access medicines under Article 31 following the Doha Declaration, and that 51 CLs have been issued for government use.[67] Countries who have used CLs include developed countries such as the U.S and Italy, as well as DCs68 and LDCs[69] such as Ecuador, Brazil, Indonesia, India, Thailand, Malaysia, Kenya, Mozambique, South Africa, Eritrea, Zimbabwe, Cameroon, Zambia and Ghana.[70] In several of these instances - particularly in African states - it remains ambiguous whether any local production occurred postgrant.[71] Article 31bis has been used successfully once - the Canada-Rwanda license - whereas the India-Nepal attempt failed. When successfully granted, CLs have reduced prices and increased medicinal access in all these cases.

To cite an example, in 2003, when the Malaysian government granted CLs for two HIV/AIDS medications, the price decreased from $365 per patient per month to $115. Zimbabwe also reported a 50% price reduction in one HIV/AIDS drug following a CL. After India's licence, the drug became available at approximately one-tenth of the original price.[72]

Due to a lack of information publicly available, assessing the impact of CLs in LDCs carries difficulties. CLs in India, Thailand and Brazil have procured medicines for millions of patients.[73] For example, Brazil's CL for Efavirenz provided treatment for 75,000 additional patients,[74] while Thailand's CL for Efavirenz increased patient access from 4539 to 29,360, and its CL for Lopinavir/Ritonavir, from 69 to 6200.[75]

But affordability does not guarantee accessibility, as citizens' wages and States infrastructure, governance and health distribution abilities also impact access.[76] The health sector in DCs and LDCs is particularly susceptible to corruption, which manifests in both the public and private sector, thereby affecting drug allocation.[77] The devastating effects of health care corruption on health outcomes and public health obligations notably prompted, and were reflected in, a UN Special Rapporteur report in 2017.[78] Enforcing measures to combat corruption is thus necessary for the results of CLs to be enjoyed equally. Price reductions caused by CLs also accrue government savings, which may be used to strengthen health systems against corruption. For example, after its license, Brazil saved approximately $30 million annually for its health procurement budget.[79] However, the emergence of FTAs greatly threatens the feasibility of using, and even initiating CLs.

49 Reichman, "Comment," 248.
50 Ibid.
51 For a more detailed historical account see Ellen FM 't Hoen, "TRIPS, Pharmaceutical Patents and Access to Essential Medicines: A Long Way from Seattle to Doha" Chicago International Law Journal (2002): 27.
52 Paragraph 4 of the Doha Declaration.
53 Paragraph 6 of the Doha Declaration.
54 General Council, "Decision of 30 August 2003 Implementation of Paragraph 6 of the Doha Declaration on the TRIPS Agreement and Public Health," WT/L/540 and Corr.1, 1st September 2003.
55 WTO News Items, "WTO IP Rules Amended to Ease Poor Countries' Access to Affordable Medicines," 23rd January 2017; General Council, "Decision of 6 December 2005 on Amendment of the TRIPS Agreement," WT/L/641, 8th December 2005.
56 Frederick M. Abbott, "The Trips-Legality of Measures taken to Address Public Health Crises: Responding to USTR-State-Industry Positions that Undermine the WTO" in The Political Economy of International Trade Law: Essays in Honor of Robert E. Hudec ed. Daniel L. M. Kennedy and James D. SouthWick (Cambridge: Cambridge University Press, 2002): 313.
57 Amir Attaran, "Assessing and Answering Paragraph 6 of the Doha Declaration on the TRIPS Agreement and Public Health: The Case for Greater Flexibility and a Non-Justiciability Solution," Emory International Law Review 17, (2003): 746 – 748; Carlos M. Correa, "TRIPS Agreement and Access to Drugs in Developing Countries," Emory International Law Review 17, no. 2 (2003): 36.
58 Article 31bis para 2(a)(i) of TRIPS; Article 3 in Annex to TRIPS.
59 Ibid, para 2(b)(ii)-(iii)-(c).
60 Ibid.
61 Kenneth C. Shadlen, et. Ad., "Globalization, Intellectual Property Rights, and Pharmaceuticals," 17.
62 Carolyn Deere, The Implementation Game: The TRIPS Agreement and the Global Politics of Intellectual Property Reform in Developing Countries, (Oxford: Oxford University Press, 2009): 92-93; WIPO, "Survey on Compulsory Licenses Granted by WIPO Members to Address Anti-Competitive Uses of Intellectual Property," CDIP/4/4/REV.Study/INF/5, 4th October 2011, Table 2.
63 Deere, The Implementation Game, 20.
64 WTO Decision of the Council for TRIPS, "Extension of the Transition Period under Article 66.1 for LDC Members," IP/C/64 12th June 2013.
65 For a complete list, see: http://unctad.org/en/Pages/ALDC/Least%20Developed%20Countries/LDC-Map.aspx (accessed Mar. 25, 2018).
66 Ellen FM 't Hoen, et. ad., "Medicine Procurement and the Use of Flexibilities in the Agreement on Trade-Related Aspects of Intellectual Property Rights, 2001-2006" Bull World Health Organ 96, (2018): 185.
67 Ellen FM 't Hoen, Private Patents and Public Health: Changing Intellectual Property Rules for Access to Medicines (Amsterdam: Health Action International, 2016): 54, 58.
68 As identified by the UN in the report, "World Economic Situation and Prospects 2018," 106 – 130.
69 As identified by the UN Committee for Development Policy, "List of LDCs as of June 2017.
70 Donald Harris, "TRIPS After Fifteen Years: Success or Failure, as Measured by Compulsory Licensing," Journal of Intellectual Property Law 18, no. 2 (2011): 388.
71 Hiroko Yamane, Interpreting TRIPS: Globalisation of Intellectual Property Rights and Access to Medicines, (UK: Hart Publishing, 2011): 313-316; Deere, The Implementation Game, 83.
72 Dipika Jain and Jonathan J. Darrow, "An Exploration of Compulsory Licensing as an Effective Policy Tool for Antiretroviral Drugs in India," Health Matrix 23, no. 3 (2013): 442.
73 Petra Moser and Allessandra Voena, "Compulsory Licensing: Evidence from the Trading with the Enemy Act," American Economic Review 102, no. 1 (2012): 396.
74 Dr. Pedro Canisio Binsfield, Ministry of Health of Brazil "The Use of Compulsory License as Patent Related Flexibility – The Brazilian Experience in Health," Regional Seminar for Certain Latin American and Caribbean Countries on the Implementation and Use of Several Patent-Related Flexibilities," February 2012, 20.
75 Hein and Moon, Informal Norms, 100-107.
76 Richard A. Epstein & F. Scott Kieff, "Questioning the Frequency and Wisdom of Compulsory Licensing for Pharmaceutical Patents," The University of Chicago Law Review 78, no. 1 (2011): 81-82.
77 Saskia Mostert, et al., "Corruption in Health-Care Systems and its Effect on Cancer Care in Africa," Lancet Oncology 16, no. 8 (2015): 394-404.
78 Report of the UN Special Rapporteur on the Right of Everyone to the Enjoyment of the Highest Attainable Standard of Physical and Mental Health, UN General Assembly, A/72/137, UN 72nd Session, 14th July 2017.
79 Public Interest, "Post-TRIPS Examples" 2.

3.2. Bilateral and multilateral trade agreements

Bilateral and multilateral FTAs between countries commonly include conditions surpassing TRIPS requirements - so-called 'TRIPS-plus provisions' - that restrict the grounds on which countries may issue CLs.[80] Article 1(1) of TRIPS permits States to enter into FTAs with IP standards exceeding those under the treaty, provided these agreements do "not contravene" TRIPS provisions. As CLs are an option available to countries and not a requirement, these agreements do not conflict with TRIPS *per* se.[81]

Provisions limiting CL grounds are present in FTAs between the EU and Columbia, Peru, South Korea and Moldova.[82] Moreover, the EU has proposed similar restrictions during FTA negotiations with India, Thailand, Vietnam and Myanmar.[83] These provisions are additionally included in FTAs between the US and other countries. For instance, the US-Jordan FTA confines CL use in Jordan to failure to work patents, to remedy anti-competitive behaviour and for public health emergencies and public non-commercial use.[84] US FTAs with Chile,[85] Morocco,[86] Bahrain,[87] and the signatories of the Central American-Dominican Republic FTA,[88] (Guatemala, El Salvador, Honduras, Costa Rica, Nicaragua and the Dominican Republic), allow patent owners to essentially consent to a CL before it may take effect, by requiring patentee consent or acquiescence for a party to bring a patented product to market.[89]

FTAs indirectly, but intentionally, restrict CLs by including clauses that: prolong patent rights; impose 'non-reliance principles', include stringent market provisions,[90] and extend data exclusivity periods.[91] Consequently, generic manufacturers cannot utilise the clinical trial and safety data in the original patent application, and the data originator must authorise and give market approval for products subject to a CL.[92]

Moreover, evidence suggests that FTAs increase drug prices and decrease access.[93] After the US-Jordan FTA, prices increased by 20%.[94] It is estimated that the U.S-Colombia FTA will increase medical expenditures in Colombia by $919 million by 2020[95] and that the U.S-Peru FTA will limit medical access for 700,000 people.[96] Thus, TRIPS-plus provisions may hinder the market entry of medicines irrespective of a CL, and impair affordability and accessibility.

NGOs, scholars and politicians have led harsh criticisms against FTAs in this respect.[97] Former French President Chirac at the 2004 International AIDS Conference in Bangkok stated that, "making certain countries drop these measures (TRIPS flexibilities) in favour of bilateral trade negotiations would be immoral blackmail."[98] Although countries 'willingly' sign FTAs, they financially rely on trade benefits and preferential market treatment.[99] As such, developed countries use FTAs to advance stronger IP standards outside TRIPS and arguably arrange for a *quid pro quo*; restriction of TRIPS flexibilities in exchange for preferential trade treatment.[100] Given the implications of FTAs, the UN Special Rapporteur discourages TRIPS-plus standards and warns *all* States to be "mindful of actions which may infringe upon the right to health."[101]

Signing FTAs that increase drug prices and limit access may violate States' obligations under the right to health and lead to situations where such obligations conflict with the right to health.[102] Tribunals which arbitrate FTA disputes have notably rejected the argument that human right obligations can legally affect how States execute their trade obligations.[103] In Suez v Argentina, the tribunal reinforced that respecting human right duties fails to justify non-compliance with trade obligations, as States "must respect both of them equally."[104] Hence, States must fulfil their trade and human right obligations simultaneously, even when they are at odds. By dichotomising these two obligations, States' duty to ensure medicinal access may have no influence in FTA arbitrations should CLs be challenged. This may engender conflicting decisions between national courts, FTA tribunals and the WTO, which not only creates legal uncertainty for States but could promote forum shopping.[105]

Clauses permitting health exceptions in FTAs are ambiguous, weakening "their use as a defence."[106] Certain FTAs or FTA side letters explicitly refer to the Doha Declaration,[107] which may allow for FTAs to be interpreted and implemented in a manner supportive of CLs given the purpose of the Declaration.[108] However, this depends on how the legal value of the side letters is interpreted, as well as the language present in FTAs.[109] If language from the Declaration is 'transplanted,' this provides a stronger case than if it is merely referenced.[110] Whether countries will challenge FTAs likewise depends on their willingness to do so in light of the possibility of backlash, retaliation, or the removal of trade concessions. Thus, as FTAs may effectively force countries to choose between trade benefits or health measures, FTAs will likely have grave implications for public health and pose a serious challenge to the viability of CLs.

3.3. Investor-state arbitration proceedings

Trade agreements also allow firms to sue countries for alleged TRIPS violations,[111] as they include a clause permitting Investor-state arbitration proceedings (ISAPs), where a foreign company may bring suit against a country for TRIPS breaches that affect their IP investments in an independent tribunal, as firms are ineligible to use the WTO Dispute Settlement Mechanism (DSM).[112]

To cite an example, in *Eli Lily v Canada*, Eli Lily raised a claim under the North American Free Trade Agreement (NAFTA) by alleging that Canada's invalidation of its patents diverged from NAFTA requirements.[113] Patentability criteria under NAFTA notably mirror those of TRIPS.[114] Canada revoked Eli Lily's patents as they failed to comply with Canada's promise doctrine, that the invention achieves what it promises to do in its patent application; a TRIPS flexibility.[115] The Tribunal unanimously dismissed Eli Lily's claims, but on evidentiary grounds, not because TRIPS flexibilities do not apply in investment disputes.[116] It is therefore possible for firms to initiate action against a country using CLs by claiming the license compromises their IP investments.[117]

This development invites two problems. First, it may curb countries' rights to procure medicines through the use of TRIPS flexibilities, and discourage countries from granting CLs lest they have to pay substantial financial damages.[118] Eli Lily notably claimed $500 million in remuneration.[119] Although a case involving CLs has yet to arise, leaked documents addressed to the Colombian Ministry of Trade revealed that Novartis threatened to initiate ISAPs when Colombia considered issuing a CL for Glivec in 2016, by claiming that the CL violated the Swiss-Colombian bilateral investment treaty.[120] Colombia consequently abandoned the CL.

Second, it may create conflicting WTO and Investor-State tribunal (IST) decisions on TRIPS flexibilities.[121] ISTs are not bound by WTO rulings, nor by previous Tribunal decisions which are often contradictory, inconsistent and without possibility of appeal.[122] In other words, a CL may be reinforced by the WTO panel, yet the country may be required to reimburse the firm by an IST. Damages awarded by the two judicial bodies also differ, as WTO reports usually instruct the country to amend the conflicting law in question, whereas ISTs require financial compensation.[123] The lack of balance between actors in investor-state disputes is also recognised by developed countries and caused Belgium to challenge this procedure, which is permitted under the EU-Canada Comprehensive Economic and Trade Agreement (CETA), to the Court of Justice of the EU.[124] Given these circumstances, a UN Trade and Development Conference report found that these "disputes pose particular challenges for host States and especially DCs."[125]

80 Bryan Mercurio, "TRIPS-Plus Provisions in FTAs: Recent Trends," in Regional Trade Agreements and the WTO Legal System ed. Lorand Bartels and Federico Ortino (Cambridge: Cambridge University Press, 2006): 231.

81 Henning G. Ruse-Khan, "The International Law Relation Between TRIPS and Subsequent TRIPS-Plus Free Trade Agreements: Towards Safeguarding TRIPS Flexibilities?" Journal of Intellectual Property Law 18, no. 2 (2011): 349-350.

82 Health Action International and MSF, "Empty Gestures: The EU's Commitments to Safeguard Access to Medicines," Review of the European Union's Trade & Investment Policy (2015): 4, 13.

83 Ibid; European Commission, "Overview of FTA and other Trade negotiations," Updated March 2018.

84 Article 1.2 of U.S-Jordan, FTA, 24th October 2000, 41 I.L.M 63; Carlos M. Correa, "Multilateral Agreements and Policy Opportunities," in Intellectual Property Rights: Legal Economic Challenges for Development ed. Mario Cimoli, et. al., (Oxford: Oxford University Press, 2014): 431.

85 Article 17.10(b) of U.S-Chile, FTA, 6th June 2003, 42 I.L.M 1026.

86 Article 15.10(4) of U.S-Morocco FTA, 15th June 2004, 44 I.L.M 544.

87 Article 14.9(4) of U.S-Bahrain FTA, 14th September 2004, 44 I.L.M 544.

88 Ch 15 of U.S-Dr-Central America-Dominican Republic FTA, (CAFTA-DR), FTA, 5th August 2004, 19 U.S.C.

89 Harris, "TRIPS After Fifteen Years," 394.

90 Yamane, Interpreting TRIPS, 504-505.

91 Ruse-Khan, "The International Law Relation," 32.

92 Sam F. Halabi, "Multipolarity, Intellectual Property, and the Internationalization of Public Health Law," Michigan Journal of International Law 35, no. 4 (2014): 752; WHO, "Guide for the Application," 19.

93 Lisa Forman, "The Inadequate Global Policy Response to Trade-Related Intellectual Property Rights: Impact on Access to Medicines in Low- and Middle-Income Countries," Maryland Journal of International Law 31, no. 1 (2017): 13.

94 Oxfam International, "All Costs, No Benefits: How TRIPS-Plus Intellectual Property Rules in the US-Jordan FTA Affect Access to Medicines," (2007): 2.

95 UN Development Programme and UNAIDS Issue Brief, "The Potential Impact of Free Trade Agreements on Public Health," (2012): 4.

96 Forman, "Trade Rules, Intellectual Property," 342.

97 Pedro Roffe and Christoph Spenneman, "The Impact of FTAs on Public Health Policies and TRIPS flexibilities," International Journal of Intellectual Property Management 1, No. 1 (2006): 76-77.

98 Message from M Jacques Chirac, President of the Republic, Read by M Xavier Darcos, Delegate for Cooperation, Development and Francophony, 15th International AIDS Conference, Bangkok, 13th July 2004; Yamane, Interpreting TRIPS, 505.

99 Roffe and Spennemann, "The Impact of FTAs," 79; Ruse-Khan, "The International Law Relation," 349.

100 Ibid.

101 UN Special Rapporteur 2009 Report, para 108.

102 General Comment 14 of ICESCR; Simon M. Walker, The Future of Human Rights Impact Assessment of Trade Agreements, (Intersentia Publishing, 2009): 66, 68; Forman, "Trade Rules, Intellectual Property," 342-343.

103 Urbaser S.A et al., v Argentine Republic, ICSID Case No. ARB/07/26, 8th December 2016, para 1210.

104 Suez et al., v Argentine Republic, ICSID Case No. ARB/03/19 30th July 2010, para 262.

105 Ho and Gathii, "Regime Shifting," 4, 10.

106 Halabi, "Multipolarity, Intellectual Property," 751.

107 U.S FTA with Chile;

108 Ruse-Khan, "The International Law Relation," 354.

109 Christoph Spenneman, Interview, 14th May 2018: Appendix A.

110 Ibid., 357-358.

111 Christopher Gibson, "A Look at the Compulsory License in Investment Arbitration: The Case of Indirect Expropriation," American University International Law Review 25, no. 3 (2010): 359, 394-399.

112 Article 22 of Understanding on Rules and Procedures Governing the Settlement of Disputes.

113 Eli Lily and Company v Government of Canada, ICSID Case No. UNCT/14/2, 16th March 2017.

114 NAFTA, Can-Mex.-U.S, December 17, 1992, 32 I.L.M, 289 (1993), Article 1709.

115 Eli Lily and Company v Canada, para 303, 307.

116 Cynthia M. Ho, "A Collision Course Between TRIPS Flexibilities and Investor-State Proceedings," UC Irvine Law Review 22, no. 395 (2016): 102-104.

117 Ibid.

118 WTO, "Intellectual Property and Public Interest," para 7.

119 Eli Lily v Canada, para 467(i).

120 For documents, see: https://www.publiceye.ch/fileadmin/files/images/Gesundheit/Zwangslizenzen/ISDS_Threat_Novartis_against_Colombia.pdf (accessed Mar. 23, 2018); Ho, "A Collision Course," 174-175.

121 Ho, "A Collision Course," 102-104.

122 Ibid.

123 Ibid, 397.

124 European Parliament, "CETA Ratification Process: Latest Developments," October 2017, http://www.europarl.europa.eu/RegData/etudes/ATAG/2017/608726/EPRS_ATA(2017)608726_EN.pdf; Koninnkrijk België, "CETA: Belgian Request for an Opinion From the European Court of Justice, https://diplomatie.belgium.be/sites/default/files/downloads/ceta_summary.pdf. (Both accessed May 7, 2018).

125 UNCTD, "Investor-State Disputes: Prevention and Alternatives to Arbitration," at 3-4.

Over 3000 of these agreements exist, with Investor-State disputes increasing over time and, correspondingly, WTO disputes declining.[126] Ho affirms that ISAPs impair TRIPS flexibilities' potential to protect public health and "indicate an intent to shift from the WTO/TRIPS regime to the use of investment disputes to effectuate policy changes in domestic and global laws."[127] However, as ISAPs on CLs have yet to arise, determining conclusively the extent that ISAPs will influence CLs is subject to dispute. That being said, the reasoning for the decision in *Eli Lily v Canada* and the financial damages claimed gives serious cause for concern. Paying $500 million in damages may devastate a DC or LDC's health resources and prevent the procurement of medicines, as well as justify non-compliance with obligations under the right to health due to a lack of financial means.[128] Thus, if a tribunal finds that a CL amounts to expropriation under an FTA, by restricting or discharging IPRs considered an investment, and whereby private actors may claim compensation,[129] a chilling effect on use under both Article 31 and 31bis may arise and curtail the right to access affordable medicines.[130]

It is worth mentioning that, on the 20th of March 2018, the EU announced that negotiations for the establishment of a multilateral court designated to adjudicate disputes under EU investment treaties is underway.[131] This Court may create a more democratic process in resolving such disputes by appointing judges, following Court procedures and allowing appeals.[132] However, until this court comes into being, an assessment of how it will impact ISAPs and CLs can only be limited.

In sum, while CLs can protect the right to health and enable medicinal access, the proliferation of FTAs with ISAPs constitutes a significant barrier to their effective use. Against this background, CLs seem an infeasible way of increasing medicinal access. However, following Article 31*bis*, CLs are indeed frequently 'used' - in another sense - to improve public health. Thus, issuing or threatening to issue a CL has proliferated the issuance VLs.[133]

4. DEFINING VOLUNTARY LICENSES

VLs – also known as 'social licenses' – of patented pharmaceuticals are private contractual agreements between right holders and second parties, which stipulate the terms and conditions for the entry of particular medicines in a designated market.[134] Two types exist. First, 'out-licensing', where the right holder licenses an already developed drug or the technology to produce the respective drug. Such arrangements typically grant second parties with the production, marketing and distribution rights of an invention, whereby the right holder is rewarded with royalty payments from net sales.[135] The second type is 'in-licensing,' where the right holder licenses a compound at a pre-clinical or clinical stage, which the generic manufacturer develops and introduces to the market in exchange for royalties.[136]

VLs are not subject to the conditions under Article 31 of TRIPS. Instead, terms such as royalties, exclusivities and geographical preferences are negotiated between the parties: a generic firm, State or the MPP; and the patentee, typically a pharmaceutical company. Of the top 20 pharmaceutical companies globally, Gilead, GSK,[137] Boehringer Ingelheim (BI), Bristol-Myers Squibb, Merck Inc., Johnson & Johnson, Hoffman La Roche and Abbvie license their products voluntarily.[138] A reported total of at least 47 VLs for different drugs have been granted; 19 attributed to Gilead.[139] VLs primarily arise through the MPP or from bilateral agreements.

4.1. Bilateral Voluntary Licensing Agreements

Bilateral VL agreements are negotiated between the parties directly. The know-how and rights to manufacture and distribute the drug are transferred to generic companies, who sell the medicine under the original label or another brand name. As a result, local manufacturers may access drug technology that is otherwise unavailable, as well as acquire the competency to produce medicines of safe quality.[140] For example, Gilead licenses a multiple compound used to treat Hepatitis C. The license is non-exclusive, non-sublicensable, non-transferable and demands a 12% royalty of net sales for products sold in Malaysia, Thailand and Ukraine, and 7% for products sold in the other permitted countries. The licensee must also purchase active pharmaceutical ingredients (APIs) from Gilead approved suppliers, although local manufacturers produce the product.[141] VLs are also negotiated through the MPP, an organisation attempting to bridge the gap between pharmaceutical companies and the governments of DCs and LDCs, as well as generic manufacturers.

4.2. The Medicines Patent Pool

The UN-funded MPP is the only patent pool dedicated to licensing pharmaceuticals in DCs and LDCs.[142] The MPP aims to improve access to HIV/AIDS, tuberculosis and malaria treatments.[143] The WIPO defines the model of patent pools as "an agreement between two or more patent owners to license one or more of their patents to one another or to third parties."[144] In short, the MPP obtains licenses from patent-holders and then sub-licenses manufacturing and distribution rights to generic companies. A significant advantage of MPP licenses is their data exclusivity waivers, which guarantees that generics may be registered in licensed territories.[145]

A total of 17 product licenses with 20 generic manufacturers were signed by the MPP between 2011-2018.[146] For example, in 2014, ViiV Healthcare and the MPP signed an agreement to license Dolutegravir, a 1st line HIV drug, in both adult and paediatric formulations. The adult license permits the sale of Dolutegravir in 92 named countries, and the paediatric license, in 121 named countries without royalties.[147] If a generic firms sells the drug in 10 other countries, a 5-10% royalty prevails.[148] Brazil is excluded and most South American countries may only sign paediatric licenses. Notwithstanding the implications of such geographical limitations, which are discussed in section 4.4.4, the license proved beneficial in terms of price and access.

4.3. Findings in relation to price & medicinal access

Outcomes demonstrate that drug prices fall precipitously following VLs. This is confirmed in the 2016 Final Report by United Nations Secretary-General's High-Level Panel on Access to Medicine, which found that these agreements have reduced treatment costs in several countries.[149] Due to the VL between Gilead and Strides, the price of Tenofovir in India dropped from $200 per patient, per year to $26.[150] As a result of the price decline initiated by another Gilead VL, access to an HIV/AIDS drug increased from 30,000 persons in 2006 to 8.7 million in 2015.[151] Gilead's VLs also stimulate competition within the market and cause non-licensees to decrease prices.[152] The level of competition initiated by VLs is notably decisive of how much prices decline post-license.[153] As bilateral VLs are primarily confidential, data on their effect on price and access is limited. In contrast, licenses signed through the MPP are publicly available.

[126] UNCTD, "Investor-State Disputes: Prevention and Alternatives to Arbitration," at 3-4..
[127] Ibid; Ho, "A Collision Course," at 109; James Gathii and Cynthia Ho, "Regime Shifting of IP Law Making and Enforcement From the WTO to the International Investment Regime," Minnesota Journal of Law, Science and Technology 18, (2017): 5, 16.
[128] Hestermeyer, Human Rights, 111-112.
[129] Christoph Spenneman, Interview, 14th May 2018: Appendix A; Carlos M. Correa, "Investment Protection in Bilateral and Free Trade Agreements: Implications for the Granting of Compulsory Licenses," Michigan Journal of International Law 26, no. 1 (2004): 345-348.
[130] Yamane, Interpreting TRIPS, 504-505.
[131] Council of the EU, "Multilateral Investment Court: Council Gives Mandate to the Commission to Open Negotiations," Press Release 144/18, 20th March 2018.
[132] Christoph Spenneman, Interview, 14th May 2018: Appendix A; EU Council, Declassified Version of Note from General Secretariat of the Council to Delegations Regarding "Negotiating Directive for a Convention Establishing a Multilateral Court for the Settlement of Investment Disputes," 12981/17, 1st March 2018, para 9, 10.
[133] Harris, "TRIPS After Fifteen Years," 395.
[134] Peter Beyer, "Developing Socially Responsible Intellectual Property Licensing Policies: Non-exclusive Licensing Initiatives in the Pharmaceutical Sector," in Research Handbook on Intellectual Property Licensing ed. Jacques de Werra (Cheltenham: Edward Elgar Publishing, 2013): 228.
[135] K. D. Raju, "Compulsory v Voluntary Licensing: A Legitimate Way to Enhance Access to Essential Medicines in Developing Countries" Journal of Intellectual Property Rights 22, (2017): 27.
[136] Tahir Amin, "Voluntary Licensing Practices in the Pharmaceutical Sector: An Acceptable Solution to Improving Access to Affordable Medicines?" I-MAK, (2007): 3.
[137] GSK Public Policy Position, "IP & Access to Medicines," provided by GSK via email, https://www.gsk.com/media/2958/ip-atm-developing-countries-policy.pdf (accessed May 14, 2018).
[138] AstraZeneca, Novo Nordisk, Bayer, Merck KGaA, Pfizer, Sanofi, Sankyo, Takeda, Astellas, Eisai, Eli Lilly and Novartis have yet to license their patents; Peter Beyer and WHO, "Enhancing Access to Medicines through Licenses" WIPO Regional Seminar for Certain African Countries on the Implementation and Use of Several Patent-Related Flexibilities, 29th – 31st January 2013: 11; Access to Medicine Index, "Access to Medicine Index 2016 Overall Ranking," 8-11, 63-77.
[139] Raju, "Compulsory v Voluntary Licensing," 27.
[140] Amin, "Voluntary Licensing," 12.
[141] For license, see: http://www.gilead.com/-/media/files/pdfs/other/form%20ar%20hcv%20license%20agmt%20gild%2011202017.pdf?la=en (accessed Mar. 1, 2018).
[142] UNAIDS Press Statement, "UNAIDS Welcomes First VL to the MPP and Pharmaceutical Company,"12th July 2011.
[143] MPP, "Annual Report 2016: Expanding for Better Treatment Options." https://annual-report-2016.medicinespatentpool.org (accessed Apr. 1, 2018).
[144] WIPO, "Patent Pools and Antitrust – A Comparative Analysis" Prepared by the Secretariat, March 2014: 3.
[145] T Hoen, Boulet and Baker, "Data Exclusivity," 4.
[146] Data obtained from MPP, https://medicinespatentpool.org/who-we-are/our-model/ (accessed Apr. 2, 2018).
[147] AmfAR, "HIV Treatment Clinical Brief: Dolutegravir," September 2017.
[148] AmfAR, "HIV Treatment Snapshot: Dolutegravir, May 2017.
[149] UN High-Level Panel on Access to Medicines Report, 8, 22.
[150] Murphy Halliburton, India and the Patent Wars: Pharmaceuticals in the New Intellectual Property Regime (Cornell: Cornell University Press, 2017): 96.
[151] Tanoubi Ngangom, "Voluntary Licensing: Access to Markets for Access to Health," Observer Research Foundation Report (2016): 7.
[152] Information obtained from article provided by Gilead via email: Kasturi Rangan and Katharina Lee, "Gilead Sciences, Inc. Access Program," Harvard Business School, 3rd February 2010: 15.
[153] Michael A. Friedman, Henk den Besten and Amir Attaran, "Out-licensing: A Practical Approach for Improvement of Access to Medicines in Poor Countries," The Lancet 361, (2013): 241.

TABLE 2: INFORMATION ON ALL MPP SUB-LICENSES.[154]

Patented Drug	Disease	Patentee	Countries Included	Persons with Disease Covered	# of Sublicensees (Generic Firms)
Abacavir	HIV	ViiV	121	99.3%	1
Atazanavir	HIV	Bristol Myers	122	89 %	6
Bictegravir	HIV	Gilead	116	89.8%	8
Cobicistat	HIV	Gilead	116	89.8%	7
Daclatasvir	Hepatitis C	Bristol Myers	112	65.4%	10
Dolutegravir (Adult)	HIV	ViiV	92	94	14
Dolutegravir (Pead.)	HIV	ViiV	121	99 %	13
Elvitegravir	HIV	Gilead	109	88.4%	4
Emtricitabine	HIV	Gilead	112	92.2%	11
Lopinavir	HIV	Abbvie	Africa	Africa	7
Lopinavir (Pead.)	HIV	Abbvie	125	98.8%	1
Darunavir	HIV	U.S NIH	N/A	N/A	N/A
Raltegraiv (Paed.)	HIV	Merck Sharp	92	98%	2
Ravidasvir	Hepatitis C	Pharco	19	N/A	Not yet finalised
Solid Drug	HIV	U. of Liverpool	137	N/A	Not yet finalised
Sutezolid	Tuberculosis	John Hopkins	238	N/A	Not yet finalised
Tenofovir Alafenamide	HIV	Gilead	116	89.8%	11
Tenofovir Disoporxil	HIV	Gilead	112	89 %	3

The MPP boasts VLs for 17 products, and 80 sub-licenses with 19 manufacturers.[155] Following MPP sub-licenses, HIV and Hepatitis C drugs experienced an average 89% price drop.[156] As a result, the MPP distributed more than 4.7 billion dosages of lower-priced HIV/AIDS drugs between 2011-2018, and reached 99% of children and 87%-91% of adults living with HIV in DCs and LDCs.[157] 125 countries have received essential medicines.[158] In total, the MPP serviced approximately 10.9 million patient years from January of 2012 to June 2016.[159] A study estimates that, by 2027, a cumulative 36 million patient years will access lower cost drugs due to MPP VLs.[160] Moreover, the study found that the direct savings generated by the MPP is expected to reach $2.3 billion by 2028, "equivalent to more than 24 million people living with HIV receiving first-line antiretrovirals (ARVs)" in DCs and LDCs "for 1 year at average prices today."[161]

VLs can therefore benefit the national economy by boosting savings and stimulating the local generic industry. Local production, in turn, helps concoct new drug formulations or processes by improving the proprietor's invention, which may depress the price further. This incentivises future licensing discussions and builds goodwill between generic firms and pharmaceutical companies; relations which may otherwise be strained.[162] It is also worth noting that VLs do not instigate adverse reactions from foreign States or pharmaceutical companies.[163] However, a downside to VLs is, as Table 2 displays, that they remain focused on HIV/AIDS drugs, with less frequent use in relation to other medications.

4.4. Focusing on particular diseases

A study conducted in 2007 found that all but one of the 32 VLs from 2003 to 2005 in India and Africa concerned HIV/AIDS.[164] A 2017 review ascertained that out of the total 47 VLs granted, 40 concerned HIV/AIDS drugs, 3 Cancer, 2 Hepatitis B&C,[165] 1 Avian Flu and 1 for Tamiflu.[166] Of the 18 patents currently licensed through the MPP, 15 are for HIV drugs.[167] These results confirm that VLs remain predominantly directed towards HIV/AIDS. The focus on HIV/AIDS is due to the severity of the disease, but it may also be owed to downstream effects from CLs, which tend to concentrate on HIV/AIDS drugs (Table 1), albeit not to the same degree as VLs. Omitting licensing possibilities for other diseases is a shortcoming of VL schemes, as the WHO estimates that Non-communicable diseases (NCDs) kill 38 million people in low- and middle-income countries annually.[168] Cancer notably accounts for 5.3 million of the deaths in DCs, which means it now claims more people than malaria, tuberculosis and HIV/AIDS combined.[169] Persons living with HIV/AIDS are also increasingly dying from hepatitis C and tuberculosis co-infections. Cryptococcal meningitis, a co-infection, accounts for 15% of all AIDS-related deaths, whereby 181,000 of the 223,100 infected annually die.[170]

The MPP is looking to expand into NCDs in the future, but as they follow the WHO essential medicines list (according to which non-profit organisation UNITAID determines which medicines it will fund), they are prevented from broadening their medicinal scope.[171] Global funding for diseases other than HIV/AIDS, tuberculosis and malaria is, in general, scarce and firms remain reluctant to license drugs for other diseases. However, efforts to widen VLs' medicinal scope are experiencing some progress. One recent bilateral VL concerned drugs for Hepatitis C and certain cancers.[172] UNITAID currently has an open call for cervical cancer proposals and is seeking to expand further into NCDs.[173] The MPP also confirmed the feasibility of expanding into other essential medicines on the 24th of May 2018, and announced in 2017 that it will continue working with the WHO to determine which products should be prioritised for in-licensing for another three years.[174] As the WHO expanded its list to include several cancer medicines in 2017, VLs may include more cancer drugs, although there remains a dearth of WHO recommendations for other NCDs, cardiovascular and endocrine medicines.[175] Given the focus on VLs for HIV/AIDS treatments, and the MPP's observation of the WHO list, CLs remain a useful tool to enable access to medicines for diseases excluded from VLs. CLs are, furthermore, crucial as certain terms and conditions constrain the potential for VLs.

4.5. Terms & Conditions

VL agreements, irrespective of the number of parties involved, share similar factors which may impede access to medicines. This is due to terms and conditions which impose certain restrictions, demand high royalties, include geographical constraints, and lack transparency.

4.5.1. Lack of transparency

A preliminary issue facing VLs is the lack of transparency in agreements. As most licensing contracts signed through the MPP are now publicly available on their website, this issue pertains to bilateral VL agreements. Bilateral VL agreements are often confidential, notwithstanding the snippets of information shared through press releases. This presents two significant difficulties. First, as previously mentioned, it encumbers the process of assessing the impact certain licenses have in relation to medicinal prices and access. Second, it disadvantages local manufacturers and governments as they may accept less favourable terms than other parties.

To help parties negotiate prices, it is suggested that they consult the annual medicine price list published by Clinton Health Access Initiative (CHAI), a non-profit organisation furthering the cause of improving health access by decreasing medical prices.[176] This list includes drug information and the price offered by four different pharmaceutical companies, as CHAI partners with firms such as Pfizer and Cipla,[177] and brokers "market access agreements," also known as price reduction schemes. It is worth noting such international procurement schemes may achieve lower prices for HIV/AIDS drugs than CLs,[178] and that generic drugs produced in India are frequently sold at a lower price than those offered through a VL.[179] The CHAI price list may therefore help governments decide whether a CL or VL (or neither) is the best option.

Checking the MPP online database 'MedsPal,' which presents information on 6,800 national patents and licenses in more than 110 countries, can also assist parties when discussing royalties by providing bargaining power if the patent soon expires.[180] Reviewing MPP sublicenses is likewise an option as it exposes parties to current terms and conditions, and can function as a template when discussing bilateral VLs. Another alternative is conferring with regional patent offices to inquire about information on existing licenses. For example, the African Regional IP Organisation, an intergovernmental body that facilitates collaboration on IP matters among 19 African States.[181] Cooperation between countries is vital, so parties conclude VLs with fair conditions.

[154] Information obtained from sublicenses published on MPP website, https://medicinespatentpool.org/what-we-do/global-licence-overview/licences-in-the-mpp/. (accessed Apr. 2, 2018).
[155] MPP, "Update on Progress of MPP Sub-Licensees," January 2018, https://medicinespatentpool.org/uploads/2017/09/Update-on-Progress-of-MPP-Sub-licensees-January2018.pdf (accessed Apr. 2, 2018).
[156] Ibid.
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[161] Ibid, 1, 10.
[162] Halliburton, India and the Patent, 98.
[163] Frederick M. Abbott, and Graham Dukes, Global Pharmaceutical Policy: Ensuring Medicines for Tomorrow's World, (Cheltenham: Edward Elgar, Publishing, 2009): 144.
[164] Amin, "Voluntary Licensing," 7 – 10.
[165] Gilead, "Expanding Chronic Hepatitis C Treatment in Low- and Middle-Income Countries," (2017) http://www.gilead.com/-/media/files/pdfs/other/hcv-access-fact-sheet-011217.pdf (accessed Mar. 18, 2018).
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[171] Maica Trabanco, Interview, 28th March 2018: Appendix A.
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[181] See: http://www.aripo.org (accessed Apr. 9, 2018); See also WHO, "WHO Support for Medicines Regulatory Harmonization in Africa: Focus on East African Community," WHO Drug Information 28, no. 1 (2014): 11-13.

4.5.2. Restrictions

Due to the lack of transparency, second parties may unknowingly allow for more restrictive provisions than neighbouring countries. As a result, agreements contain varying terms and conditions. Common restrictions include designating suppliers from which ingredients must be sourced and stringent obligations in case of improvements.[182] Capping the number of patients to be treated is also mentioned as a limitation present in VLs,[183] as well Gilead's 'anti-diversion programme' which requires patients to disclose sensitive personal information such as, name, address and citizenship to receive treatment.[184] This may prevent persons who are refugees, homeless or without stable living arrangements to access medicines.[185]

Furthermore, requiring licensees to purchase materials from certain suppliers may prevent prices from falling further. Gilead, for example, attaches supplier specifications to all its licenses.[186] Although this protects medicinal quality, it increases opportunity costs by imposing higher production expenses when other companies sell equivalent ingredients at a lower price for the identical quality. This also forces several manufacturers to import ingredients, which may carry additional VAT costs.[187] More seriously, controlling the sourcing of APIs can curb generic competition in the long-run.[188]

In addition to this, if manufacturers improve products, numerous agreements require the licensee to sublicense back the new formulation indefinitely and royalty free. Of the 18 sub-licensing agreements signed through the MPP, 16 include such a condition. For instance, in the MPP sub-license for Viiv's drug 'Abacavir,' clause 8.1. stipulates that if, during the agreement, the licensee "makes, develops, acquires, reduces to practice, becomes entitled to or secures control over any Improvements it shall communicate such improvements to Licensor and Viiv".[189] Moreover, it obliges the licensee to grant Viiv and the Licensor a "perpetual, irrevocable, worldwide, royalty-free, non-exclusive license to use any Improvement, Improvement Patent and related know-how."[190] Such a perpetual and royalty free 'grant-back' may discourage manufacturers from signing licenses or innovating, which benefits both parties.[191] Given this, a royalty-bearing grant-back should be sought and is present in at least one MPP sublicense: the agreement regarding the combination drug 'Lopinavir/Ritonavir' for the paediatric population. The sublicense provides that AbbVie retains the sole right to *purchase* the potential new formulation from the sublicensee or to license the new product until the termination or expiration of the original agreement, while paying a 4% royalty of net sales.[192] Similarly to brand companies, generic manufacturers should be rewarded for their innovation and willingness to share technology in the form of royalties.

4.5.3. Royalties

Royalties in VLs reportedly reach an average of 5%,[193] albeit increasing when agreements cover greater territory or new products.[194] This is significantly higher than CLs, whose rate ranges from 0.5% to 4%. Although royalties in licenses not related to CLs and VLs primarily remain undisclosed, a survey reviewing agreements between the top 15 pharmaceutical companies estimates that they average anywhere between 0-25%,[195] depending on the drug's stage of development.[196] A 5% rate may therefore represent a reduction compared to other licensing deals. However, manufacturers often incorporate the 5% rate in their price.[197] As a result, patient expenses, which are usually paid for out-of-pocket due to a lack of health care, increase.[198] Costs furthermore accumulate as HIV/AIDS patients may require several treatment stages of ARVs, as well as inhibitors and medicines for co-infections.[199]

One plausible means of lowering royalties is to threaten right holders with CLs or attempt to sublicense through the MPP. Post MPP negotiations decreased the royalties of several pre-existing bilateral VL agreements with Gilead for the drug Tenofovir from 5% to 3%.[200] Although less common, certain MPP licenses have resulted in agreements forgoing royalties and permitting free technology transfer, as well as assistance if necessary.[201] If this occurs, generic firms should be wary of the licensor attaching other restrictive clauses to offset such lenient conditions. However, this solution is futile for countries that are excluded from MPP licenses or VLs altogether.

4.5.4. Geographical exclusions

Excluding certain countries from agreements or imposing geographical constraints on where manufacturers may sell products restricts access to medicines in those regions. DCs deemed middle-income, which by definition still constitute DCs, are primarily precluded from VLs[202] as they are profitable markets for pharmaceutical companies.[203] By doing so, pharmaceutical companies may charge higher prices on medicines in these areas.[204] Brazil, Colombia, Mexico, Venezuela and China are, for example, routinely excluded.[205] Consequently, the lowest prices of medicines are inaccessible to these countries, despite housing 75% of the world's impoverished.[206] MPP licenses include 55-80% of middle income countries.[207] As a result, ARVs licensed through the MPP are currently unavailable to 7 million people living with HIV/AIDS.[208] The MPP notably discloses that negotiating the geographical scope with patent holders carries the greatest difficulties.[209] This demonstrates that the financial interests inciting the adverse reactions to CLs also influence how VLs are administered.

Countries tackle the issue of geographical exclusion differently. South Africa challenged, as well as resolved, its exclusion through national competition law. The South African *Competition Commission* found that GSK and BI had abused their dominant position by pricing their patented HIV/AIDS drugs exorbitantly.[210] The parties entered into a settlement agreement that required the two companies to voluntarily license their patents to generic manufacturers.[211] In the case of GSK v Competition Commission, this agreement was reinforced.[212] As a result, firms licensing their patents through bilateral VLs or the MPP increasingly include South Africa in their geographical scope.[213]

Threatening with a CL is also used to leverage patent holders to expand their geographical scope. For instance, Gilead included Malaysia, Ukraine, Belarus and Thailand in a VL only after the Malaysian Cabinet approved a CL for the reference drug.[214] Granting a CL likewise ensures that a country attains access to the drug in case of unwavering exclusion. Additionally, certain MPP sublicenses allow for generics produced under a VL to be supplied to countries excluded from the license, if they issue a CL or there is no patent infringement.[215]

As of now, this opportunity has never been put to practice, despite its potential to improve medicinal access. Employing this measure successfully requires the consolidation of several factors. The same drug would need to be unavailable in both countries, and the countries would need to cooperate and facilitate export and import. While the structure of the license notably mimics that of Article 31bis, it escapes its legislative, procedural and administrative hurdles, and can procure a more favourable price. This is because the VL/CL combination involves several countries, helping to achieve economies of scale. Keeping this in mind, this license may provoke resistance from the patentee as its products would be reaching a country that may have been intentionally excluded. The country issuing a CL, likely to be a middle-income DC, may thus encounter similar international opposition as when granting a 'regular' CL.

Nevertheless, the possibility of executing this VL/CL license through the MPP and the criticism these exclusions elicit exerts pressure on pharmaceutical firms to extend their geographical reach. Indeed, the general trend demonstrates that companies are progressively including middle-income countries.[216] However, as VLs also preclude upper-middle-income countries, they fail to improve medicinal accessibility and affordability in these regions. CLs therefore remain necessary for countries prevented from the enjoying the benefits of VLs.

[182] Ibid; AmfAR, The Foundation for AIDS Research, "Improving Voluntary Licensing Agreements for Better Drug Access," 16th November 2017.
[183] Germán Velásquez, Carlos Correa and Robert Weissman, "Cost-Containment Mechanisms for Essential Medicines, Including Antiretrovirals, in China," WHO Health Economics and Drugs No. 13, (2002): 7.
[184] For more information, see MSF Briefing: https://www.msfaccess.org/sites/default/files/HepC_Gilead_anti-diversion_ENG_2014_0.pdf (accessed Apr. 10, 2018).
[185] Ibid.
[186] Amin, "Voluntary Licensing," 14.
[187] Osewe, Nikrumah and Sackey, Improving Access to HIV/AIDS, 35.
[188] AmfAR, "Improving Voluntary."
[189] MPP, "License Agreement for Abacavir – Paediatrics," February 2013: 7.
[190] Ibid.
[191] Beyer, "Developing Socially Responsible," 240; Article 40 of TRIPS notably also provides that grant-back provisions may be deemed anti-competitive.
[192] MPP, "License Agreement for Lopinavir, Ritonavir (LPV/R) Paediatrics" November 2014: 7.
[193] Amin, "Voluntary Licensing," 4.
[194] Beyer and WHO, "Enhancing Access to Medicines through Licenses," 15.
[195] Nigell Borshell and Adrian Dawkes, "Pharmaceutical Royalties in Licensing Deals: No Place for the 25 Per Cent Rule of Thumb," Journal of Commercial Biotechnology 16, (2010): 10.
[196] Sharon Finch, "Royalty Rates: Current Issues and Trends," Journal of Commercial Biotechnology 7, (2001): 6.
[197] Amin, "Voluntary Licensing," 14.
[198] Striner, "Learning From Practice," 559.
[199] WHO Fact Sheet, "What's New in HIV Treatment," November 2015: 1-2.
[200] Juneja, et al., "Projected Savings," 9.
[201] Ibid; Amin, "Voluntary Licensing," 4.
[202] MSF, "Untangling the Web of Antiretrovirals Price Reductions" 17th edition July 2014; See for example, Gilead, "Scaling Up Antiretroviral Treatment Sustainably" November 2016, 4, http://www.gilead.com/-/media/files/pdfs/other/hiv%20access%20backgrounder%20us%20112816.pdf (accessed Feb. 27, 2018).
[203] Beyer, "Developing Socially Responsible," 238.
[204] MSF, "Johnson & Johnson/Tibotec AIDS Drug Licenses Leave Out Too Many Patients," Press Release 28th January 2011.
[205] AmfAR, "HIV Treatment Snapshot: Dolutegravir," May 2017; Halliburton, India and the Patent, 112.
[206] Ibid.
[207] Information obtained in PowerPoint presentation supplied by the MPP.
[208] Halliburton, India and the Patent, 112.
[209] Maica Trabanco, Interview, 28th March 2018: Appendix A.
[210] Beyer, "Developing Socially Responsible," 232.
[211] Ibid.
[212] GlaxoSmithkline v Competition Commission, Case 61/CAC/Apr06, Competition Appeal Court, 12/06/2006.
[213] MSF, "Untangling the Web of Price Reductions," 11-12.
[214] MPP Press Release, "The MPP and Gilead Sciences Sign License for Bictegravir," 4th October 2017.
[215] 'T Hoen "Medicine Procurement" 189.
[216] Beyer, "Developing Socially Responsible," 238, 242.

4.6. Additional factors to consider

As VLs are predominantly regulated by the pharmaceutical industry, remedying the aforementioned terms and conditions presents a challenge and is up to individual countries. Assessing the circumstances from which VLs emerge is therefore vital to evaluate how VLs may improve or impede access. This will help decipher whether VLs represent a means to alleviate public health problems by counteracting the issues of CLs or are a means to retain control over patented inventions.

4.6.1. Prolonging patent lives & security?

It is claimed that companies voluntarily license base compounds protected by weak or soon-to-expire patents to strategically elude patent revocations.[217] What is noticeable is that patents may be placed in the MPP after Patent Offices reject patent applications.[218] Likewise, bilateral VLs may be signed after patent applications fail. To cite an example, Gilead signed VLs with seven Indian generic companies only after the Indian Patent Controller rejected Gilead's patent application for the Hepatitis C medicine Sofosbuvir in 2015.[219] This creates the impression that certain VLs serve the purpose of facilitating for companies to retain market power by signing agreements, which secure financial rewards with potential competitors otherwise eligible to enter the market independently, as opposed to resolving medicinal inaccessibility.[220]

Products not yet patent protected may also be licensed, which may indicate certain VLs merely arise as attempts to evade patent opposition.[221] For example, in 2007, Gilead agreed to license Tenofovir, an HIV/AIDS drug awaiting patent registration, with 11 Indian manufacturers.[222] The license granted the manufacturers with rights to produce and distribute Tenofovir in ninety-five countries in exchange for a 5% royalty, along with two additional conditions.[223]

First, that the product not be sold in certain countries, such as Brazil and China; and second, that all materials had to be purchased from Gilead approved suppliers. These restrictive conditions caused Cipla to reject Gilead's licensing offer and submit a pre-grant opposition to the patent office in India, who rejected Gilead's patent application due to evergreening in 2009.[224] As a result, generic versions of Tenofovir became available at $700 per patient, per year, a significant reduction from its previous price of $5,718 per patient in DCs annually.[225] These examples therefore suggest that companies may license questionable patents, and that an intention behind VLs is to obviate legal challenges.

Conversely, ex ante estimating a patent application's success is an intricate task with uncertainty involved.[226] This uncertainty weakens claims that VLs are merely negotiated as a defence measure. VLs also involve 'viable' products with newly acquired patent protection. MedsPal shows that the expiry date of patents licensed varies anywhere from 2018 to 2032.[227] It is therefore implausible that licensors generally only licence patents they predict to fail. Indeed, while revoked or failed patents may grant more advantageous terms for generic manufacturers, opposing patents or seeking revocations may prolong medicinal inaccessibility, as these proceedings often experience delays and appeals, and are costly.[228] Additionally, using an inventor's know-how also saves firms from having to develop their own technology, enabling the product to become available more quickly. Thus, it may prove more beneficial overall to exploit the information provided by VLs.

India may be an exception, given their vigorous patent opposition procedure which is less time consuming than fellow countries and permits third parties to file pre-grant observations.[229] In one instance, this process led to GSK rescinding a patent application and thereby allowing Indian generic manufacturers to offer Abacavir to DCs and LDCs for $330 per patient, per year. This is a price 31% lower than its expected rise following the potential patent (as a data point, Abacavir is sold in Mexico for $2,600 per patient, per year).[230] Pre-grant oppositions can, as with the tactic of threatening right holders with CLs, be used as a method to increase VLs or reduce prices.[231] Licensees should therefore perform sufficient due diligence on the patent subject to a potential VL, as it may help to negotiate better terms, determine whether to avoid the license altogether, or issue a CL.

4.6.2. Merely a means to avoid compulsory licenses?

Whether VLs as used by pharmaceutical companies as a form of corporate social responsibility, or whether they are merely a means of avoiding CLs, is subject to speculation. VLs accord inventors with greater control over compensation, and when they are to be issued, than CLs. This, in turn, entails that manufacturers and countries retain less control over whether they are to be included in an agreement, which medicine is to be supplied and, most importantly, when that medicine will be supplied. Meanwhile, CLs grant extensive power to licensees with regards to royalties, products and timing, and are unfavourable to patent holders compared to VLs. The emergence of VLs is thus cited as the reason for lower CL use in recent years.[232] A study of all CLs from 2001 to 2016 found that of the 19 proposed CLs that were ultimately not issued, 5 resulted in bilateral VLs.[233]

VLs may indicate companies' willingness to cooperate with countries to increase access to medicines. This reasoning is supported by the fact that VL negotiations have been a preliminary requirement to issue a CL since the ratification of TRIPS in 1995, and VLs only recently proliferated. Additionally, countries increasingly sign VLs with the MPP without threatening or issuing CLs. Companies are also progressively taking independent steps to alleviate public health issues, such as participating in price reduction schemes with NGOs.[234] Alternatively, the underlying reason for the correlation between lower CL use and the increase of VLs could simply be that it offers firms a means to escape a CL. One criticism of VLs is that such a 'friendly measure' helps companies refute the necessity of CLs more convincingly.[235] In other words, VLs may represent pharmaceuticals companies choosing the carrot to keep the stick, CLs, at bay.

This criticism hinges on the fact that VLs frequently arise after countries threaten with a CL. For example, Gilead included Malaysia in a VL only after Malaysia issued a CL,[236] despite Malaysia attempting to acquire a VL through the MPP and with the patent holder directly.[237] Roche similarly signed a sublicense with a company and selected 12 other potential generic manufacturers after Taiwan issued a CL for Tamiflu.[238] Also, in Kenya, GSK and BI granted a VL for HIV/AIDS drugs only after Cosmo, a local manufacturer, applied for a CL.[239] Cosmo attempted to negotiate a VL before its CL application. Upon signing the agreement, both companies dropped the price of their drug below Cosmo's in the same market.[240] Not only does this imply that the companies acted in bad faith and in an ethically unsound manner, but it undermines the credibility of VLs and discourages parties from seeking such a license.

Hence, inventors unwillingly grant *voluntary* licenses *voluntarily*. By averting CLs and agreeing to VLs, firms maintain market control and their influence on royalties. Correspondingly, achieving favourable terms is reported as an obstacle while negotiating VLs.[241] LDCs, for instance, have less bargaining power given their small market size. Meanwhile, Brazil, who has a large pharmaceutical market, monitors which diseases require intervention and then uses CLs as a bargaining chip by threatening with issuances to depress prices.[242] Issuing or threatening with CLs is thus a method of spurring VLs. However, this 'tactic' leads to superfluous negotiations and needlessly protracts the process at the expense of the patient. Indeed, it may be idealistic to expect patentees to voluntarily share information without the threat of a less favourable outcome. However, VLs present firms with an opportunity to increase revenue by entering untapped markets.[243] It is estimated that the African market may generate $30 billion in revenue for pharmaceutical companies.[244] As generic manufacturers have stable supply chains in DCs and LDCs, companies can widen their market reach with VLs in these regions with little investment.[245] Therefore, threats should not be necessary, as VLs achieve a middle ground by offering incentives for all parties involved.

[217] Amin, "Voluntary Licensing," 4-5.
[218] Halliburton, India and the Patent, 134.
[219] Gilead Press Release, "Gilead Announces Generic Licensing Agreements to Increase Access to Hepatitis C Treatments in Developing Countries," September 15th 3014.
[220] WHO, "Cost-Containment -Mechanism" 7.
[221] Beyer, "Developing Socially Responsible," 236; Amin, "Voluntary Licensing," 13.
[222] Lalitha, "TRIPS Flexibilities," 114.
[223] Ibid.
[224] Ibid.
[225] Ibid.
[226] Ramanujam and Goyal, "One View of Compulsory Licensing," 404.
[227] Data obtained from MPP MedsPal Database, see: www.medspal.org (accessed Mar. 10, 2018).
[228] Amin, "Voluntary Licensing," 12.
[229] Tahir Amin, "Re-visiting the Patents and Access to Medicines Dichotomy: An Evaluation of TRIPS Implementation and Public Health Safeguards in Developing Countries," in The Global Governance of HIV/AIDS: Intellectual Property and Access to Essential Medicines ed. Obijiofor Aginam, John Harrington and Peter K. Yu (Cheltenham: Edward Elgar Publishing, 2013): 118.
[230] Ibid.
[231] Yibeltal Assefa, et al., "Access to Medicines and Hepatitis C in Africa: Can Tiered Pricing and Voluntary Licencing Assure Universal Access, Health Equity and Fairness?" Globalization and Health 13, no. 73 (2017): 8.
[232] Beall and Kuhn, "Trends in Compulsory," 6.
[233] 't Hoen, "Medicine Procurement," 186.
[234] McNeil Jr, "As Cancer Tears Through Africa."
[235] Ho, Access to Medicine in the Global Economy, 365 – 366.
[236] Gilead Press Release, "New License Agreement with the MPP for Access to Bictegravir," 4th October 2017.
[237] Director-General of Health Malaysia, "Implementation of the Rights of Governments for Sofosbuvir Tablet to Increase Access for Hepatitis C Treatment in Malaysia," 20th September 2017.
[238] Amanda Mitchell, "Tamiflu, the Takings Clause, and Compulsory Licenses: An Exploration of the Government's Option for Accessing Medical Patents," California Law Review 95, no. 2 (2007): 544.
[239] Osewe, Nikrumah and Sackey, Improving Access to HIV/AIDS, 33.
[240] Olulomire Ogunye, et. al., "AIDS, Africa and ARVs: Domestic Production as the Solution to the treatment Gap," in Global Challenges: Science and Society, 2009: 14.
[241] 't Hoen, Boulet and Baker, "Data Exclusivity," 3.
[242] Singhai and Singhai, "A Study of," 23.
[243] Daniel D. Kim, "Voluntary Licensing of Pharmaceuticals: The Strategy Against Compulsory Licensing," American University Intellectual Property Brief 8, no. 1. (2016): 68, 104.
[244] Ngangom, "Voluntary Licensing: Access," 8.
[245] Ibid.

Procuring agreements with threats also raises ethical concerns and fails to alleviate tensions between pharmaceutical firms and countries. Cooperation between these parties is not only essential to preserve public health and increase access to medicines in a sustainable manner, but to motivate firms to undertake R&D for diseases afflicting DC and LDCs. Despite these implications, VLs do contribute to remedying medicinal inaccessibility and, as stated by Ho, "serve as an example of how the alternative solutions, although not completely satisfying, nevertheless promote more access to medicines."[246]

5. CONCLUDING THOUGHTS

Affordability is a key factor to improve access to medicines in DCs and LDCs, and to protect the right to health. Both VLs and CLs serve as a means to reach this end, albeit through vastly different routes and with different results. Which license ultimately engenders the better price for the public depends upon a plethora of factors, including the license duration, the product itself, the technology licensed, whether it is for import or local manufacturing, costs of APIs, exclusivities, generic availabilities, royalty rates and so on. CLs allow for competitors who reach production costs nearing zero per-unit level, and who price correspondingly, to penetrate the market. For VLs, prices vary depending on whether it is an agreement between a patentee and one generic manufacturer, several manufacturers, or through the MPP. If the VL is non-exclusive, thereby involving several generic firms, the resulting spurring of competition can depress prices significantly. However, if the VL is with one manufacturer, in the absence of competition, drug costs remain mostly intact. The amount of competition in the market is thus a determining factor as to which license achieves a more favourable price.

However, as shown, the process of acquiring the rights to use a pharmaceutical patent is likewise crucial to the success of the license in procuring access to medicines. This relates to both the administrative and legislative procedure of obtaining a license, as well as the aftermath. Middle-income DCs may encounter resistance both internationally and domestically when issuing CLs, whereas LDCs have yet to report similar occurrences. VLs are not accompanied by such social, economic or trade-related consequences and may therefore, for political reasons, be preferential depending on the country.

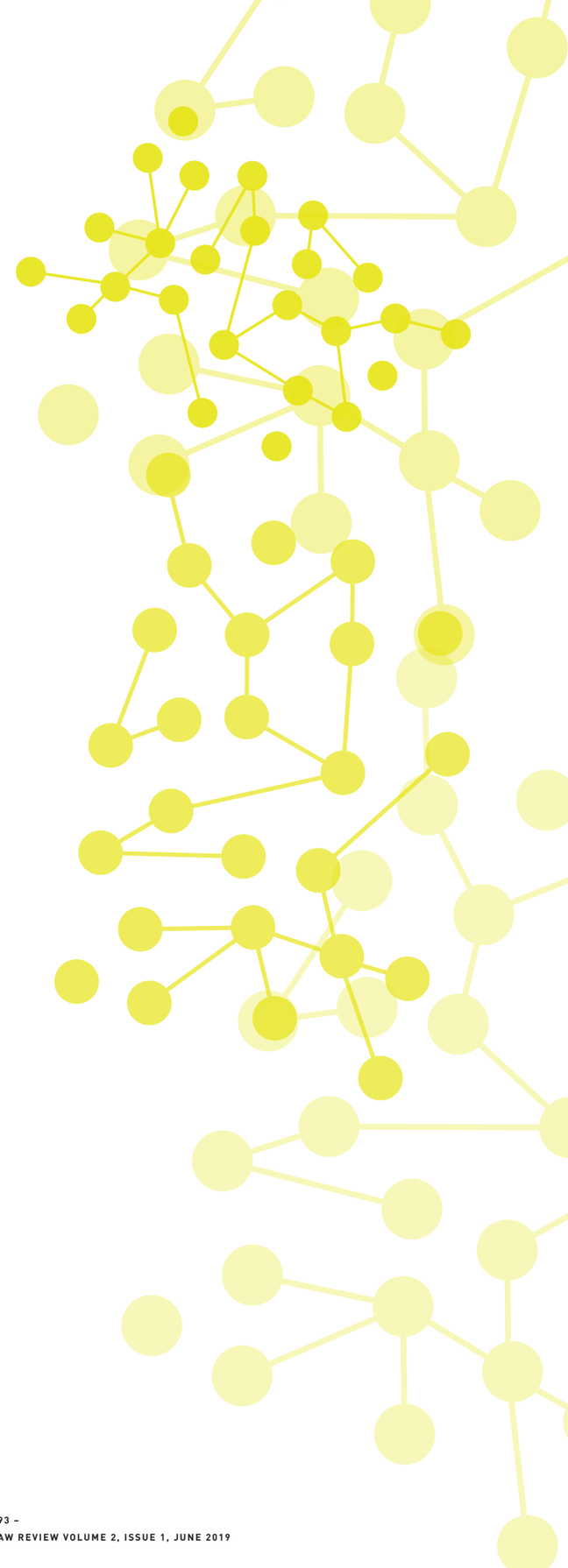
Procedurally, both licensing options may meet obstacles. Constraints present under TRIPS and in national laws inhibit the process of issuing a CL under both Article 31 and 31bis. Although several licenses were indeed successful and experienced no issues, an advantage of VLs is nevertheless that the process includes fewer procedural difficulties and is less strenuous and time-consuming than CLs. VLs also meet minimal resistance from pharmaceutical companies and foreign States, diminishing the threat of litigation and political pressure. However, several countries struggle to obtain VLs and sign licenses only after threatening to issue or issuing a CL or, alas, are never included in the geographical scope of the license. The geographical exclusions present in several VLs reinforces the relevance of CLs and the necessity of using both licensing options.

The type of treatment to be licensed is equally important and particularly germane to HIV/AIDS, as persons are required to consume multiple medicines with enhancers or boosters. MPP sublicenses allow parties to combine products encompassing several patents, saving parties from seeking a license for each patent individually, and saving patients from purchasing several different drugs. CLs increasingly include the ARV cocktail, but this is contingent on what is patented in each respective country. This issue continues to be relevant as future drugs may contain the ARV compound, as well as boosters, and compounds able to treat co-infections and HIV/AIDS simultaneously, or several lines of HIV/AIDS treatments. Global populations are increasingly becoming resistant to 1st line drugs and, as India enforced the TRIPS standards in 2005, there are fewer generics available.[247] The inability to secure 2nd and 3rd line HIV/AIDS drugs may therefore develop into an issue tantamount to the level of medicinal inaccessibility present during the first AIDS epidemic 'outbreak.' Securing treatments for NCDs, tropical diseases and furthermore must also be prioritised. As the results of CLs and VLs of HIV/AIDS drug demonstrate, these licenses significantly improve access to medicine for citizens of DCs and LDCs. Should similar efforts be employed for other diseases, medicines could become more readily available and so public health issues capable of being remedied from the outset; not in hindsight where the consequences of omission are the needless deaths and suffering of millions of persons, annually.

In conclusion, although CLs enable medicinal access, the extent of which Articles 31 and 31bis succeeds in protecting the right to health by increasing access to medicines in DCs and LDCs is limited by the resistance of foreign States and pharmaceutical companies, in addition to FTAs procedural difficulties which impair the possibilities of issuing CLs. VLs escape the restrictions of FTAs, as well as the threat of foreign retaliation and procedural inefficiencies hindering CLs. However, VLs remain focused on HIV/AIDS drugs and frequently exclude middle-income DCs. VLs should therefore not supersede CLs, despite its advantageous process, as the extent to which VLs improve access to medicines is confined to its stated geographical limits and to a limited range of diseases. For countries and diseases excluded, VLs fail to remedy the issue of inaccessible medicines in DCs and LDCs. Given this, CLs should be used by States to counteract these deficiencies. In this way, CLs and VLs should be used in a complimentary manner to offset each other's limitations, to cover the range of diseases in question, and to reach the citizens in all countries of need, thereby maximising medicinal access and protecting the right to health.

[246] Ho, Access to Medicine in the Global Economy, 367.

[247] Ravinda K Gupta, John Gregson and Silvia Bertagnolio, "HIV-1 Drug Resistance Before Initiation or Re-Initiation of First-Line Antiretroviral Therapy in Low-Income and Middle-Income Countries: A Systematic Review and Meta-Regression Analysis" (2018) Lancet Infectious Disease 18 346, 346-350.



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PERSPECTIVE

In Pursuit of Robinson Crusoe:

Pharmaceutical Naming from the Lab to the Pharmacy

By Kristina Björnerstedt and Gunnel Nilsson

With more than ten years within pharmaceutical name creation, Kristina Björnerstedt, Managing director and naming consultant at Skriptor Zigila, and Gunnel Nilsson, Senior Trademark Attorney at IP Law firm Groth & Co, who has more than twenty years' experience from the pharmaceutical industry will share some of their insights and experiences in the everyday challenges of pharmaceutical naming. They have worked with more than 1000 naming projects for several of the largest pharmaceutical companies such as Pharmacia, Roche, Astra Zeneca, Boehringer Ingelheim, Actavis and Bayer.

Naming pharmaceuticals is a topic that has been thoroughly investigated and buzzed around, and where the world's expertise agrees on at least one thing. With today's increasingly dense jungle of brands, combined with the famously strict regulations of authorities such as the European Medicines Agency (EMA), the US Food and Drug Administration (FDA) and the WHO (World Health Organization), the naming of pharmaceuticals is a true challenge. A series of legal, regulatory, linguistic and market-oriented hurdles must be overcome, not to mention the limited number of letters in the alphabet. However, with sufficient persistence and experience, devising a new pharmaceutical name remains feasible.

When a pharmaceutical company develops a new medicine or new medical equipment, clinical studies are performed, lasting from a few weeks, up to a year or more depending on the issue studied. These studies take place in four different phases.

In phase one, generally speaking, 20 to 80 healthy individuals (usually male) will be used to assess the safety of the product. This assessment will look at the possible side effects and pharmacological properties of a given substance. In phase two, participants with the relevant illness or condition will be recruited. At this stage, you will get your first information of the effect of treatment on the relevant disease, and which kind of dose is optimal. In phase three, a large patient group will be studied (between 200 and 3000 individuals, or even more) or longer period of time, to confirm the effects and safety of a new treatment compared to the standard treatment. If this third phase is successful, you can apply to have the treatment approved.

Lastly, in the fourth and final phase, when the product has entered the market, major studies are undertaken to identify any unusual side effects and monitor the safety, efficacy and optimal use of the treatment.

The results from these clinical studies (phase 4 excluded) form an important part of the documentation required to obtain a drug approval for sale in Europe. Approval of new drugs is almost always based on a joint decision made by several or all EU Member States.

The completion of phase three is usually the point at which the naming process commences. A team of trademark attorneys, product managers, marketers and representatives from the research department, as well as experienced naming consultants, will join forces to christen the new product with its final trade name. In doing so, certain core questions must first be answered. What is the treatment area? What does the drug do? How is it taken (orally, by injection, etc.)? How does it differ from existing products?

Once these core aspects have been settled, the focus shifts to identifying relevant key words. What kind of qualities do you want the name to conjure up in the mind of the reader? Here, marketing departments may have a tendency to be somewhat optimistic, organizing ambitious workshops asking participants to characterize a new product as a 'James Bond', a 'Flash Gordon' or a 'Mother Teresa'. It remains to be seen whether these characters' qualities as smart, strong, or soothing would significantly assist in the creation of sustainable brand names that are capable of passing the above mentioned filtering and fulfil the regulatory and other requirements names of pharmaceuticals have to comply with. It may be that these rituals to some extent support the company's internal creative processes. However, the crucial challenge remains to be conquered - the applicable legal and regulatory requirements. In other words, the challenge is devising a name that is a 'survivor' - a 'Robinson Crusoe' for each and every drug assignment.

To highlight some of the difficulties with the name creation process, we can first point to some major changes that have been made in naming practices over the years, that have contributed to the transformation of 'name creation' into 'brand creation'.

The so-called 'Damitol pattern' (names with quasi-chemical connotations, usually a three-syllable word with a banal chemical/medical ending such as -al, -yl or -in) has been the one of the major naming methods in the pharmaceutical industry. Examples of 'Damitol pattern' names include well-known products such as Bricanyl, Aspirin, Toradol, Alvedon, to name a few.

Over time, the registration of names under trademark Class 5 - a very crowded class including pharmaceuticals - has become increasingly difficult due to similarity issues. Using the 'Damitol pattern' does not provide many original alternative brand names, and the similarity with already registered trademarks is of course inevitable. In order to avoid this risk new forms of name creation were necessary. An example of such, more creative name creation methods is in fact the well-known pharmaceutical Losec, which was considered a milestone when it was launched in 1988. The name was inspired by the term 'low secretion' (related to the function of the substance) and was not related to its generic substance, omeprazole.
Furthermore, the industry became more global and thus ideally, one product name should work in most market. Names of pharmaceuticals were gradually taking the form of 'brands'.

Another development in pharmaceutical name creation is that pharmaceutical authorities have raised the standards of naming pharmaceuticals in regards to names. For example, names should not be too similar, either in speech or in writing. They must not resemble the name of generic substances other than those included in the product, and they should not promise too much. An example of how these restrictions may influence the name creative process is illustrated in the case of the name 'Brilinta' as a name for a blood thinning drug, approximately ten years ago. This name was rejected by the EMA on the basis that, among other reasons, the name was too similar to the word 'brilliant'. Consequently, while 'Brilinta' was retained as the drug name in the United States, it was renamed as 'Brilique' in Europe.

When it comes to testing names prior to registration, several tests are performed by marketing authorization authorities, such as the handwriting tests. Both the European EMA and its US counterpart, the FDA, allow doctors to write hand-written prescriptions which in fact may be the source of confusion. A name that when handwritten is too similar to another pharmaceutical will thus not be registered.

The past ten years have given rise to, once again, a change of course in the pharmaceutical naming process. In particular, the market platforms of today seem even further removed from the traditional 'branding mindset'. There are several reasons for this. Firstly, according to many industry experts, the market for medicines targeting broad welfare diseases has declined. Secondly, research into diseases such as cancer result in medicines that target mostly specific types of cancer (such as pancreatic cancer, lung cancer and breast cancer) and fewer wide-ranging medicines.

Another challenge faced by the pharmaceutical industry is the so-called INN system. INN stands for 'International Non-Proprietary Names' and identifies pharmaceutical substances or active pharmaceutical ingredients. In the United States they are called USANs. Each INN is unique and globally approved, and are considered to be public property, and therefore not covered by the IP law. INN names are what is commonly referred to as generic names or 'generics'. The INN system as it exists today was initiated in 1950 by World Health Assembly Resolution WHA3.11 and came into force in 1953, when the first list of International Non-proprietary Names for Pharmaceutical Substances was published. The cumulative list of INNs now stands at some 7000 names, a number that is growing by 120-150 new names per year, referring to the WHO's website. The recommendation is to avoid INN strains in so-called stem words. They can be placed as prefix, infix or suffix. Many of these stems are distinct and easy to avoid, but the nightmare for a name creator is that there are also two- or three-letter variants that totally lack distinctiveness, such as '-al', '-ine' or the infix '-io-'. As a further example, 'Ni', 'Nic' and 'Nico' are indispensable aspects of the word 'Nicotine', and yet 'Ni' features on the list of elements to be avoided in naming. However, this is an issue that is constantly being scrutinised and discussed. At the annual international Pharmaceutical Trade Marks Group Conference in Dubrovnik 2018, several participants specifically addressed this issue with the WHO. In our opinion, WHO ensured that they will do everything possible to make it easier for the industry among other things, and that the requirements for the double-headed INN strains will eventually be reduced, eliminated or at least mitigated.

It is however important to remember that despite all the regulatory constraints there is still space for creativity. The wonder drug for treating male impotency Levitra is

named in honour of Adi Levit, Israel's leading litigator. He works for Unipharm and about once a year invalidates a block-buster drug in Israel. His impact in the industry is enormous. The word Ra means evil and so the name of the drug means 'Levit is evil'. The name giving in this case was the direct result of one of his courtroom battles.

For more than 30 years, we have developed pharmaceutical names. One of our assignments in the 1990s, for pharmaceutical giant AstraZeneca, concerned a pharmaceutical product designed to lower cholesterol. The result was Crestor (rosuvastatin calcium), the most highly prescribed drug in the United States in 2014/2015. The inspiration for this name came from a person at AstraZeneca in Alderley, who expressed delight in the name Zestril (High Blood Pressure Medicine), based on the English word zest with the meaning of zeal, life appetite, spice. We decided to incorporate the word 'crest' - an English word meaning 'top'. From this, we developed the brand name Crestor.

A handwriting test mentioned above had an impact on the naming process of a drug produced by Takeda (known at the time as Nycomed). Under the framework of this project, we created the name Steovess for a drug developed for osteoporosis. In the United States, the FDA concluded that the name, when handwritten – could be confused with the name Atelvia, another anti-osteoporosis medicine. The letter A could in their view, be confused with any capital letter, and both names contained the letter 'v'. As a consequence, this drug had to be renamed 'Binosto' for the US market.

Another interesting name giving project concerned the registration of the pharmaceutical Lactovit in Israel. In this case, the pharmaceutical 'Lactovit', seeking registration as a body care product and Class 3 Trademark (soaps, gels, perfumery, essential oils, cosmetics, lotions for hair and skin care, creams for hair and skin care), was considered not confusingly similar to a prior registration for 'Lactofil', a Class 5 trademark (covering lotions, creams, mousses etc. for nourishment and cleaning of the skin). The adjudicating officer (see below) reasoned that consumers expect medicated products to be sold in pharmacies, whereas body care products are more likely to be sold in retail chains. As such, it was considered that consumers can easily distinguish between the marks 'Lactofil' and 'Lactovit', even if the goods covered by both marks are somewhat related.

As stated by Dr. Michael Factor (leading Israeli Patent and Trademark Attorney):

> *'Lacto' means milk. Like milk or* חלב *or* תחליב*. I cannot see any justification to allow a company to monopolize the prefix in Israel, despite it being in Latin and despite allegedly no-one using it previously as a prefix in a trademark. In Hebrew, the stress is on the final syllable not the first one as is the case in English. The similarities should be judged narrowly. The adjudicator is therefore correct and there is no real likelihood of confusion.'*

In 2001, we were engaged by Boehringer Ingelheim to develop a brand name for a new thrombin inhibitor anticoagulant preparation, with the generic name dabigatran. The individuals commissioning us desired a completely arbitrary name with up to three syllables. This was considered to be more distinctive and memorable, as well as being more well suited to meet the requirements of regulatory organisations such as the FDA and EMA. As many of the brand's competitors had named including the letter 'X' (Exanta, Arixtra, Clexane), this was also given as a possible direction. The result was PRADAXA, a purely invented name with no apparent reference to the disease, the generic name, or any dictionary word, but still distinctive and easy to pronounce in all major languages.

A relatively new and increasingly prevalent area within pharmaceutical naming is the borderland between medicine and information technology where, until recently, mainly descriptive product names or purely technical terms have been used to indicate the functionality of different products. We worked together with Context Vision, specialists in artificial intelligence and a world-leading supplier of software for the enhancement of medical images. We were assigned with developing a brand name for their new portfolio of digital decision support for pathologists that enable a faster diagnosis of eg. prostate cancer. INIFY™ was the name that was adopted chosen because it could bear a picture of both an 'overview' as well as that of an 'inner investigative details'. Of particular interest to us was that simple elements such as 'ini', corresponding to 'interior, inside' and 'ify' (which in English gives the feeling of a verb, such as in the words 'verify' and 'signify') were sufficient to meet the specific requirements set out in the client specification.

INIFY

Trademarks attract a great deal of attention and have become increasingly important in today's media noise. They also constitute a significant asset for a company, not only because they represent the products of a certain company, but also because they are a target of brand goodwill and are frequently used in market communications by pharmaceutical companies. The purpose of trademarks is to help consumers distinguish between products. However in the case of pharmaceutical products there are even other objectives that need to be taken into consideration, such as for instance patient safety. If a physician or a pharmacist confuses two medical products, such a mistake may expose the patient to great health risks.

On a personal note (KB), it is quite often a humbling experience to be part of the creative process regarding the development of names for medicines or equipment designed to minimize suffering.

In the complex world of pharmaceutical branding, where name creation is more difficult and challenging than ever, we find comfort in knowing we have done everything possible during the naming process down to every syllable, filter and legal detail to be able to create sustainable trademarks even in the future.

References: Kliniska studier Sverige, WHO, Peter Ekelund SkriptorZigila and Dr. Michael Factor, Israel Patent and Trademark Attorney.

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Gunnel is a senior consultant, specializing in trademarks with particular focus on pharmaceuticals. She works with strategies in areas that include monitoring, name creation and branding, research, risk analyses and customs survey, and she manages IP portfolios. Gunnel has many years' experience of the special regulations that apply to IP in Life Science, primarily relating to pharmaceuticals in connection with agencies such as the FDA, EMA and Sweden's Medical Products Agency. Gunnel was also the Head of Trademarks at a global pharmaceuticals corporation.

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The CJEU clarifies the effects of skinny labelling

– What uncertainties remain from a Swedish perspective?

By Sofia Bergenstråhle and Valter Gran

Case Note

INTRODUCTION

Where to draw the line between the protection of new innovations within the pharmaceutical area, on the one hand, and the generic companies' right to enter the market on the other, has been subject to discussion in patent law for a long time. The innovative pharmaceutical companies' right to exclusively capitalise on their innovative research stands against the generic pharmaceutical companies' right to compete in the EU market, which will likely result in lower prices and thereby in advantages from a social economic point of view.

1. THE CONCEPT OF SKINNY LABELLING

The main rule when the national authority is assessing a generic medicine[1] for marketing approval is that the information in the package leaflets, and in the summaries of product characteristics (SmPC), must be the same as for the original medicine of reference. However, the rule is not without exceptions. A generic applicant is permitted to "carve-out" from the SmPC of the reference medicinal product any indications protected by patents; this is commonly referred to as "skinny labelling" and is regulated in the second sentence of Article 11 of Directive 2001/83.[2] The aim of the article is to facilitate the placement of generic medicinal products on the market even if individual indications or dosage forms of the reference medicinal product are patented. This exemption is a result of the allowance of so-called second medical use patents, i.e. claims protecting secondary and later uses of known and safe substances (secondary medicinal indications). The concept of skinny labelling is used to avoid the infringement of a valid second medical use patent. However, it has not been clear in which cases skinny labelling can result in a patent infringing act, due to the fact that courts across Europe have put forward different reasonings in this respect.[3] Moreover, there are no precedential Swedish cases.

2. THE CJEU PRELIMINARY RULING

Recently, the Court of Justice of the European Union (CJEU) delivered a preliminary ruling[4] clarifying the effects of performing skinny labelling in the context of the marketing authorisation procedure. The court establishes that the applicant's or holder's communication of the omittance of certain indications covered by patent from the product information must be interpreted as a request to actually limit the marketing authorisation to indications not covered by patent. The judgment must be viewed as good news to pharmaceutical companies seeking effective protection for their second medical use patents. However, considering the national context and the specific characteristics of the Swedish regulatory system, the practival results, if any, can be questioned. However, at the very least the judgment may bring us one step closer to the answer on how to assess skinny labelling issues under Swedish law.

2.1 The dispute in the national proceedings

The main question in the national proceedings concerned the practice of the Dutch authority to publish in full on its website the package leaflets and the SmPC of generic medicinal products, instead of the carved-out version. Warner-Lambert Company (WLC), a pharmaceutical company within the Pfizer group, was marketing the medicinal product Lyrica, containing the active ingredient pregabalin. The only relevant patent still in force was covering the use of pregabalin for use of treatment of neuropathic pain. Several producers of generic medicinal products obtained marketing authorisation for pregabalin. Before placing its product on the market, one of the producers, Aurobindo, informed the authority that it did not intend to include the information relating to the treatment of neuropathic pain in the product information. Aurobindo asked if only relevant parts of the package leaflet and the SmPC could be published, but the authority refused.

WLC brought an action against the authority, claiming that their practice of publishing the full product information for e.g. Aurobindo's product constituted a direct infringement, as it offered pregabalin for sale for a patented indication, as well as an indirect infringement in that it encourages third parties to engage in infringements. WLC also claimed that the policy was contrary to Article 11 of Directive 2001/83.

The first instance court found that the full publication of product information does not constitute an infringement of the patent but is incompatible with the authority's duty of care. The judgment was appealed to the Regional Court of Appeal in The Hague, which considered that there were grounds to request that the CJEU considered the question of how Article 11 of Directive 2001/83 must be interpreted.

2.2 The CJEU's considerations of the questions referred

The parties before the CJEU, WLC and the Netherlands, both agreed that Article 11 permits an applicant for marketing authorisation, in respect of generic medicinal products, to leave out the indications still covered by patent from the product information. However, the parties had different views on how the relevant authority should treat a declaration from the applicant which indicates that it intends to opt for publication of an edited version.

At the outset, the CJEU noted the aim of Directive 2001/83, i.e. safeguarding public health, and the mandatory marketing authorisation for all medicinal products. The Court also highlighted the SmPC requirement, which allows for verification of whether a medicinal product meets the information needs of patients and health professionals, together with the provision stating that 'the competent authorities shall take all necessary measures to ensure that the information given in the summary is in conformity with that accepted when the marketing authorisation is issued or subsequently'. On the basis of these provisions, the CJEU stated first that the package leaflet and the SmPC form part of the marketing authorisation; second, that the medicinal product placed on the market must fulfil the conditions of the marketing authorisation, which must be reflected in the SmPC; and third, that the marketing authorisation holder may not amend the package leaflet or the SmPC without notifying the competent authority in order to obtain its approval.

The CJEU then turned to the exemption contained in Article 11 and stated that the provision confers on the applicant for a marketing authorisation of a generic medicinal product the option of derogating from the principle that the marketing authorisation of a generic medicinal product and that of a reference product must tally by reducing the scope of its application to indications or dosage forms which are not covered by patent law. In line with the principle of facilitating the entry of generic medicines to the community market, the CJEU reasoned that such entry should not be delayed until expiry of all patents which may include several indications or dosage forms of the reference medical product. Consequently, if a marketing authorisation applicant or holder for a generic product avails himself or herself of the option provided for in Article 11 of Directive 2001/83, then the marketing authorisation for that product covers only the indications and dosage forms which are not patented.

According to the CJEU, failure to include certain indications or dosage forms in the SmPC of generic medicinal products means that those indications or dosage forms are not covered by the marketing authorisation application. By making use of the above-mentioned option the applicant thus limits the scope of application and most

1 The term 'generic medicinal product' is defined in Article 10.2 (b) of Directive 2001/83 as "medicinal products which have 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".

2 Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use. Article 11 has been implemented in Chapter 3, Section 5 of the MPA's provisions on approval of medicinal products for sale etc. (LVFS 2006:11).

3 Regarding so-called Swiss type claims, UK courts and Dutch courts have come to different conclusions: See the UK decision in Warner-Lambert Company LLC v Generics (UK) Ltd (t/a Mylan) & Anor [2018] UKSC 56, where four of the five judges, albeit for different reasons, held that WLC's second medical use claims, if they would have been deemed valid, would not have been infringed by the sale of a skinny labelled product. See the Dutch decision in Merck Sharp & Dohme Corp. v. Teva Pharma B.V. and Pharmachemie B.V ECLI:NL:HR:2017:2807, where the Dutch Supreme Court held that a manufacturer or seller of a generic medicine infringes a Swiss type claim if it is reasonably foreseeable that the generic product will be used intentionally for treatment covered by the second medical indication patent.

4 Judgment of the CJEU on 14 February 2019, Warner-Lambert Company, C-423/17 (ECLI:EU:C:2019:125).

importantly, the national authorities do not have any discretion in that respect. The answer to the question referred by the national court was, in light of the above that the second paragraph of Article 11 must be interpreted as meaning that, in a marketing authorisation procedure, communication to the authority by the applicant or holder of a marketing authorisation for a generic medicinal product of the package leaflet or a SmPC of that medicinal product – which does not include any reference to indications or dosage forms which were still covered by patent law at the time that medicinal product was placed on the market – constitutes a request to limit the scope of the marketing authorisation of the generic medicinal product in question.

3. CONCLUDING REMARKS

The CJEU judgment clarifies the consequences of when the applicant or the holder of a marketing authorisation uses the option given in Article 11 to carve-out patented protected indications from the product information. The marketing authorisation is thereby limited to non-patented indications only. It is clear from the judgment that the mentioned article affects not only the SmPC but also the scope of the marketing authorisation itself, as they are meant to correspond. To this extent, the effects of the CJEU's preliminary ruling are clear.

However, from a Swedish perspective, a number of questions related to skinny labelling issues arise as a result of the clarifications by the CJEU. How should the judgment be interpreted with regard to the Swedish system? What are the practical results of such request to limit the scope of the marketing authorisation and what bearing, if any, will this have on the assessment of skinny labelling situations under Swedish law? Thanks to the CJEU judgment, innovative pharmaceutical companies may now find some solace in that one of the factors, which previously might have encouraged the distribution of generic medicine for a patent protected indication, i.e. in this case the practice of the Dutch authority, is no longer an issue. However, under Swedish law, a number of similar factors still remain problematic.

3.1 Swedish regulatory aspects

First, it is still unclear whether a request to limit the product information, and thereby the scope of the marketing authorisation, is in fact a guarantee which prevents the medicine from being used for indications still covered by patent protection. When the Swedish Medicinal Products Agency *(Läkemedelsverket, MPA)* approves an application for a marketing authorisation for a medicine, it shall also decide on what pharmaceutical products are substitutable for the medicine in question.[5] The substitutability is determined based on, inter alia, whether the products have the same active substance in the same amount and are otherwise medically equivalent. However, differences regarding indications stated in the product information are usually not considered by the MPA as such differences between two medicinal products would prevent substitution. Consequently, according to the MPA's present practice, a skinny labelled generic medicine may end up as substitutable with the reference medicinal product, which is used for an indication still covered by a patent, on the MPA's list of substitutable medicinal products.

Based on the list of substitutable medicinal products, the Swedish Dental and Pharmaceutical Benefits Agency *(Tandvårds- och Läkemedelsförmånsverket, TLV)* determines whether a pharmaceutical product shall be subsidised by the state, i.e. be covered by the Swedish reimbursement system, and also which product in each package size group has the lowest price to be applied during a specific period (a calendar month), the so-called 'product of the period system'. A consequence of the described system is therefore that a reference medicine could be replaced by a skinny labelled generic medicine by doctors or pharmacists for treating an indication that is patent protected – even if the generic pharmaceutical company has made use of the option under Article 11 to limit the product information, and hence limit the scope of the marketing authorisation to indications and dosage forms that are not covered by patent protection. In addition, even if the generic company would expressly communicate a desire to the relevant authority that the authority should respect the scope of the marketing authorisation, so that such contains only non-patented indications, it is doubtful due to the authorities' regulations whether this would mitigate the described risks. An aggravating factor is that the relevant Swedish authorities are not instructed to take existing patent rights into account in their assessments. On the contrary, the authorities are presumably even legally restricted to do so since their assessments are limited to certain factors given in the authorities' instructions and regulations. Moreover, doctors are always free to prescribe whatever medicine they consider to be most suitable in light of science and proven experience – regardless of which indications are covered by the SmPC or the marketing authorisation.

Second, there is another regulatory aspect which further complicates how the CJEU judgment should be viewed in the Swedish context. According to the MPA's guidelines, the following wording shall be included in the product leaflet for generic medicinal products:

> *"(Active substance) which is contained in (Product name) may also be authorised to treat other (diseases) (conditions) that are not mentioned in this product information. Ask your doctor, pharmacist or other health care personnel if you have further questions and always follow their instructions."*[6]

This so-called "blue box" text may be problematic from a patent law perspective as it obviously may be seen to open up the possibility for the authorities, the prescribing doctor and pharmacies to consider that the generic medicine may be used outside the scope of the product information and the market authorisation. It is probably safe to say that such a note, similar to the Swedish substitution assessment or the previous Dutch authority practice, may increase the risk that the skinny labelled generic medicine is used for an indication covered by patent.

3.2 Reduced risk of patent infringement?

If Article 11 does not provide sufficient safeguards, what could be done to reduce the risk of patent infringement in the situation of skinny labelling? It is clear from a case decided by the Swedish Supreme Court[7] that an application to the relevant authority regarding pharmaceutical benefits does not amount to an "offering for sale", i.e. is not a form of infringing conduct under the Swedish Patents Act. Except for that, there are, as far as we are aware of, no rulings by Swedish courts that clarify whether actions such as selling, prescribing, stocking or distributing a generic medicine for an indication covered by a patent but not comprised by the approved indication, or the package leaflet or the SmPC, would constitute infringing conduct. This is an unsatisfying degree of uncertainty that affects both generic and innovative pharmaceutical companies alike. Furthermore, it can be questioned whether the Swedish system provides sufficient protection for both the generic companies to ensure that they do not commit patent infringement as well as sufficient safeguards for the patent holder's right to exclusively distribute the medicinal product for the indication covered by a patent. To ensure a fair level of protection for the medicine market as well as for patent holders in the future, perhaps it is time for the patent system and the regulatory system to be more interactive, e.g. to allow for patent rights or medicinal indications to be taken into account by the relevant authorities. In any event, what must be achieved is the effective protection for the patent holder as well as a fair level of foreseeability for the generic company.

[5] The List of Substitutable Medicinal Products is available on the MPA's website (www.lakemedelsverket.se).
[6] Article 13, Section 3 of MPA's provisions (LVFS 2005:11) on labelling and product leaflets and the guidelines to the aforementioned regulation.
[7] NJA 2008 s. 1192 (Pfizer v STADA).

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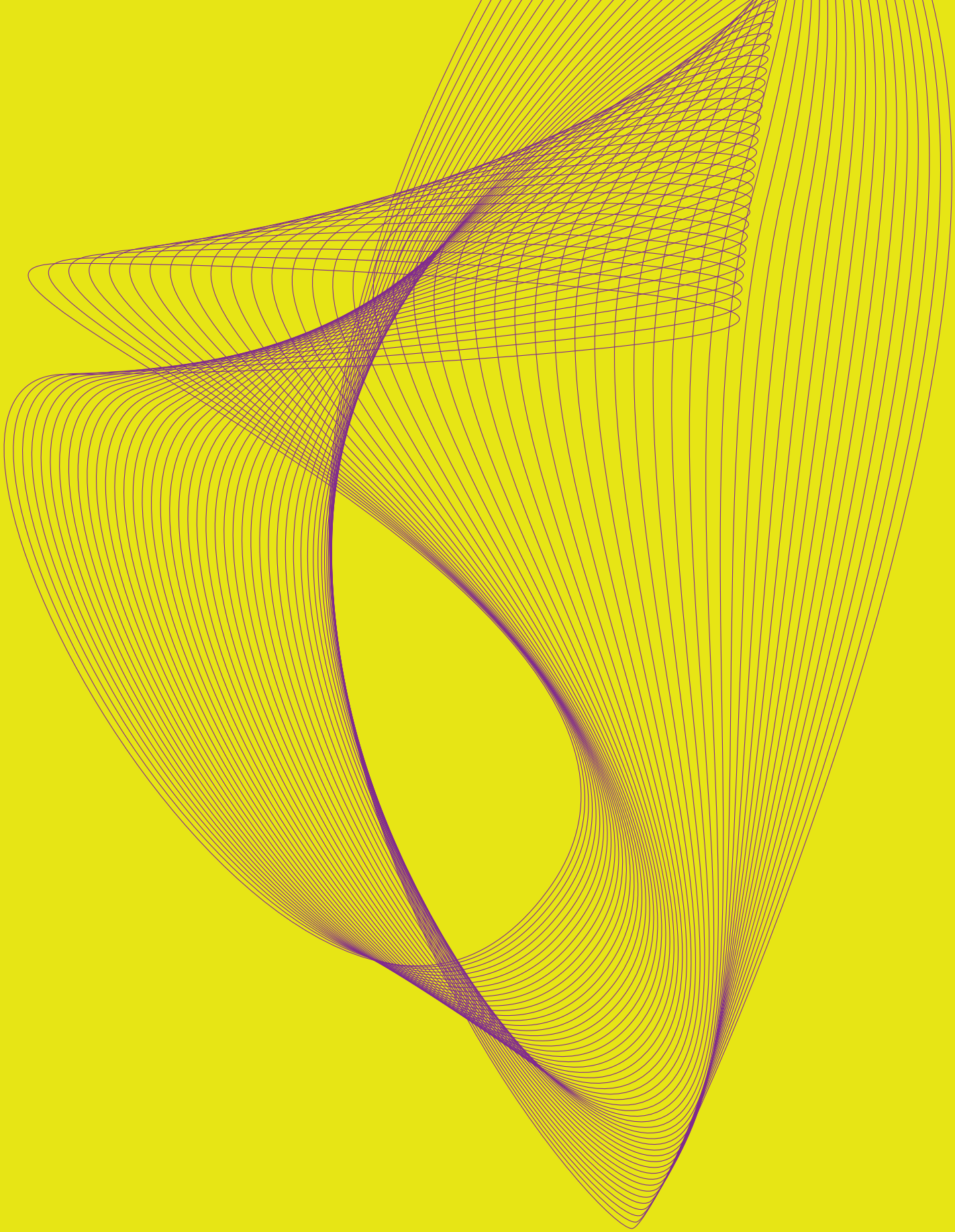

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