

Sub-setting and indication stacking in orphan drugs: a recipe for the future of exclusive rights

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1 INTRODUCTION

The present article is, apart from the result of my own work and intellectual effort, also written for a special occasion. Professor Marianne Levin has turned a healthy age, and I have been asked by the current esteemed colleagues at the Stockholm Law Faculty to write a contribution for this special occasion. Scheduling this piece of work into my calendar was difficult, due to a list of other commitments, but I could not possibly refuse the honour, so I accepted. The reader might wonder how Professor Marianne Levin and I could possibly be linked. Well, many years ago, when I was still a young (and promising) student, I undertook postgraduate master studies in Stockholm. I decided at that time, which was in 1994-1995, to write my Master dissertation about the patentability of biotechnological inventions, and Professor Marianne Levin was my supervisor. You should know that around that time, the Biotech Directive¹ was still in negotiation at the European Commission and European Parliament, and even though there was already some, mostly descriptive, literature on the subject, it was a subject which most lawyers avoided carefully, as it was perceived (and it indeed materialised) to be a very difficult subject, which required some insight into principles of biotechnology, chemistry and biology, apart from the ever so challenging and complex patent law concepts. Marianne was the best supervisor one could have imagined. She provided me with all possible assistance. I remember that one of the administrative staff members at the law Faculty was quite upset, as I could use the copy machine on the floor of the small but well stocked library of what was then called “Institutet för Immaterialrätt och Marknadsrätt”. Moreover, bad luck struck (the story of my life unfortunately) and my laptop (laptops were still a rarity those days) broke down. I was very upset about it, as it happened during the last months of my stay in Stockholm, and I had not yet developed the habit of making regular backups. I told Marianne about my misfortune, and she promptly offered her office and computer to me to continue the hard work on my Master dissertation. The only instruction was to answer the phone when it rang (in Swedish), inform the caller that she would be back the next day (also in Swedish), and inform Marianne who called. And so I did. She was also instrumental in providing me with additional funding to finalise my Master dissertation in Stockholm. After having seen some of the work I had delivered, she thought that I could handle speaking on a

conference organised by the Institute with speakers and an audience spanning the most distinguished people in IP law in Sweden (ranging from senior people at the Swedish Intellectual Property Office (PVR) over senior judges in patent law to partners and associates from some of the most prestigious law firms, and not to forget, some of the best IP academics in the country). To my own surprise, it went rather well (the only issue was that I did not have a suit, and being poor, I could not buy one for the occasion, so I had to do with a shirt and tie which I had hastily bought before the event). Having been offered that much support, I felt morally obliged to submit the best Master dissertation I could. I am sure I have even surprised Marianne when she received the final manuscript, which was no less than 380 pages (suffice to say that I exceeded the regular word limit), and I was happy to receive the highest grade for my effort. I have always kept fond memories of my time in Stockholm (even though I was poor as a student in what was then a very expensive country during pre-EURO currency and pre-EU times), and in particular also of Marianne, not only for her kindness, but also for her wit and intellect. She was (and I assume she still is) a very sharp thinker, and even though I would not want to venture into labelling character features on Swedish people, she gave me the impression of being (slightly) more direct and a “straight shooter” than most Swedes. It is safe to say that she gave me the confidence, but also the realisation that I maybe had a talent I was not aware of, i.e., that I was not the worst researcher one could find, and that realisation, together with an initial interest in doing academic research, has convinced me to continue focusing (among other things) on academic research. Whether it was a wise decision for me to become a (part-time) academic is another matter, but I will be eternally grateful to Marianne for giving me the possibility and confidence to do so.

When asked to contribute with an article, I was for a very long time in doubt what would be fitting for the occasion. I decided to go for something which is not fully mainstream and trodden path, in line also with my Master dissertation at the time in Stockholm, which covered a then very much under-researched area of the law. Having taken that decision, the choice became much easier. I decided to write about issues which are not very well researched in Europe, and which are in fact also not very well understood. So it is orphan drug exclusivities I have decided to write about here.

In this article, I want to focus on two, often intercon-

nected, features of the orphan drug exclusivity regime that require specific attention, and in my opinion also a remedy. Those features are the so-called sub-setting (also more endearingly referred to as salami slicing) and indication stacking. Even though I will explain those features more in detail in this article, I define them already briefly here so as to facilitate the further reading. Sub-setting or “salami slicing” refers to the practice of splitting certain common diseases into many ‘artificial’ subsets. Each of these subsets could then be considered a rare disease (such as certain forms of cancer). “Indication stacking” is the phenomenon where orphan products are authorised for two or more orphan indications on the market. These indications refer to distinct but sometimes also overlapping orphan conditions, and each entitles the product in question to a period of market exclusivity, which may run in parallel, with their own start and end dates.

I will demonstrate that the current regime relating to market exclusivities for orphan drugs is in need of change for future purposes. Even though there might not be a high number of cases pertaining to the practices which I will critically analyse in what follows in this article, it is my view that we should not wait to amend the regime until we are effectively confronted with a high number of such cases. We currently have around 17% of authorised orphan drugs which are the subject of indication stacking. That might not seem much, but it is better to regulate for the future than remedy for the past. To that effect, I make a number of proposals for further discussion. Some of these proposals are also options presented by the European Commission in its current evaluation of the orphan drug regime, whilst others are based on my own insights.

2 ORPHAN DESIGNATION

2.1 Introduction

For so-called orphan diseases, the definition of which will follow later in this section, one of the key problems has been, and that already for many years, how to incentivise R&D into and marketing of orphan drugs. Indeed, one of the difficult issues has been how to provide incentives to

industry to develop drugs for rare diseases. Main reason why this is a problem is that those diseases affect only small patient populations, which makes it in general not very attractive for drug developers to make the investment in developing drugs as the market will by definition be quite small. Pharmaceutical companies to a large extent use a business model where they can sell large volumes of product with hopefully, at least for some period of time, some exclusivity rights, be it patents or regulatory exclusivities,² which allows them to charge higher prices than such would be the case if there were full competition with other manufacturers. The large volumes combined with the higher than competition prices allow them not only to recoup the investment, but also take a good profit, which can be used for further R&D, and partly offsets also the losses made by failed projects.³ This is also confirmed in a recent European Commission Staff Working Document: “At the end of the 1990s, the pharmaceutical market was dominated by big companies, which were often interested in developing ‘blockbusters’ that could be sold in large volumes to tackle common diseases. By contrast, the costs of research and development meant that industry was often disinclined to invest in developing remedies for diseases with small numbers of patients.”⁴

It was perceived that traditional already existing incentives (8+2 years data and market exclusivity⁵ and patent,



¹ Directive 98/44/EC on the legal protection of biotechnological inventions, OJ L 213, 30/07/1998.

² With “regulatory exclusivities” is meant data and market protection, also called data and market exclusivity.

³ It is very difficult, if indeed possible at all, to obtain precise insight into the cost and profit structure of pharmaceutical companies, hence the profit margins and the rate of failed projects (the details of which remain largely secret and unpublished) is very difficult to discover.

⁴ COMMISSION STAFF WORKING DOCUMENT – EVALUATION. Joint evaluation of Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on

medicinal products for paediatric use and Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products, {SEC(2020) 291 final} – {SWD(2020) 164 final}, Brussels, 11.8.2020, (hereinafter COMMISSION STAFF WORKING DOCUMENT, 2020), Part 1/6, p. 10 (https://ec.europa.eu/health/system/files/2020-08/orphan-regulation_eval_sw_d_2020-163_part-1_0.pdf).

⁵ European law works with the so-called 8+2+1 system for regulatory exclusivities. There is 8 years of data exclusivity, an additional extra two years of market exclusivity (which starts at the same time as the data exclusivity, but lasts two years longer, bringing its total life span to 10 years). One additional year of

market exclusivity may be granted for new therapeutic indications showing significant clinical benefit in comparison with existing therapies (art. 10(1), para. 4); one year of data protection for new indications of well-established substances (art. 10(5)); and one year of protection for data supporting a change of classification (e.g., from prescription drug to over-the-counter) (art. 74a). These additional terms of exclusivity are not cumulative, so the total duration of protection cannot exceed eleven years. All statutory references herein are to 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 (as amended later), OJ L 311, 28.11.2001, p. 67–128.

including SPC, protection^{6,7)} for “regular” drugs were not sufficient to entice companies to invest substantially in developing drugs to fight rare diseases, reason why policy makers looked at other incentive mechanisms to ensure that more treatments were being developed for those rare diseases.

Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products,⁸ as amended by Regulation (EC) No 596/2009 of the European Parliament and of the Council of 18 June 2009,⁹ lays down procedures for the designation of medicinal products as orphan medicinal products and for the marketing authorisation of such products. The rationale for the incentives required for orphan diseases is expressed in Recital 8 of Regulation 141/2000, which reads:

“[E]xperience in the United States of America and Japan shows that the strongest incentive for industry to invest in the development and marketing of orphan medicinal products is where there is a prospect of obtaining market exclusivity for a certain number of years during which part of the investment might be recovered; data protection under Article 4(8)(a)(iii) of Council Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products [O], English Special Edition, 1965, p. 20] is not a sufficient incentive for that purpose; Member States acting independently cannot introduce such a measure without a Community dimension as such a provision would be contradictory to Directive 65/65/EEC; if such measures were adopted in an uncoordinated manner by the Member States, this would create obstacles to intra-Community trade, leading to distortions of competition and running counter to the single market; market exclusivity should however be limited to the therapeutic indication for which orphan medicinal product designation has been obtained, without prejudice to existing intellectual property rights; in the interest of patients, the market exclusivity granted

to an orphan medicinal product should not prevent the marketing of a similar medicinal product which could be of significant benefit to those affected by the condition.”

The literature recognises that many orphan diseases would not have received the appropriate treatment if there would not have been incentives provided to the pharmaceutical sector to develop treatments for those rare conditions.¹⁰

As it was said in the aforementioned European Commission Staff Working Document relating to the Orphan Drug Regulation,

“the specific objectives of the Orphan Regulation are to:

- Ensure research and development and the placing on the market of designated orphan medicinal products (availability) (specific objectives 1 and 2);
- Ensure that patients suffering from rare conditions have the same quality of treatment as any other patient (accessibility) (specific objective 3).”¹¹

A medicinal product can only be designated as an orphan medicinal product if a number of conditions are being fulfilled, which can be found in Art. 3(1) Regulation 141/2000:

“A medicinal product shall be designated as an orphan medicinal product if its sponsor can establish:

- (a) that it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand persons in the [European Union] when the application is made, or
- that it is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition in the [European Union] and that without incentives it is unlikely that the marketing of the medicinal product in the [European Union] would generate sufficient return to justify the necessary investment,

and

⁶ Under European patent law, there is 20 years of patent protection. There is additionally a maximum of 5 years of additional SPC protection, using the calculation formula laid down in Art. 13 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 (OJ L 152, 16.6.2009, p. 1–10). According to that formula, the exact SPC term, which is in effect expressed in days, is equal to the difference between the time period between the filing date of the patent and the date of grant of the marketing authorisation, minus 5 years. For example, if the patent has been filed on 1 February 2010 and the marketing authorisation for a medicinal product protected by the patent with the aforementioned filing date is granted on 1 October 2020,

the difference between the two is 10 years and 8 months. One must now subtract 5 years from that period, which is 5 years and 8 months. As the maximum term of protection for an SPC is 5 years, the SPC term for this example will be 5 years. The maximum term is 5 years, but in many cases the SPC term will be less than 5 years. There is also a one off 6 months paediatric extension upon approval of a Paediatric Investigation Plan (PIP) (Art. 36(1) of Regulation (EC) No 1901/2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004. See also Art. 13(3) Regulation 469/2009).

⁷ Under current case law, SPC protection will be very difficult to obtain for second and further medical use claims if the product which is

invoked for the SPC has already been the subject of an earlier marketing authorisation as a medicinal product, even though there might never have been an earlier patent for that product, and even if the further medical use is for an entirely different disease than the earlier marketing authorisation. See ECJ case C-673/18 *Santen SAS v Directeur général de l'Institut national de la propriété industrielle*, judgment of the Court (Grand Chamber) of 9 July 2020, ECLI:EU:C:2020:531.

⁸ OJ 2000 L 18, p. 1.

⁹ OJ 2009 L 188, p. 14.

¹⁰ V. GIANNUZZI, R. CONTE, A. LANDI, S.A. OTTOMANO, D. BONIFAZI, P. BAIARDI, F. BONIFAZI, A. CECI, ‘Orphan medicinal products in Europe and United States to cover needs of patients with rare diseases: an increased common effort is to be foreseen’

(b) that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the [European Union] or, if such method exists, that the medicinal product will be of significant benefit¹² to those affected by that condition.”

There are hence two categories of conditions that could trigger the orphan designation.

The first category is based on what is called “prevalence”, in the case of the European orphan drug designation system it means that it concerns a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand persons in the [European Union] when the application is made. The second category is based on return on investment, i.e., without incentives it is unlikely that the marketing of the medicinal product in the [European Union] would generate sufficient return to justify the necessary investment.

It appears that the vast majority of applications for orphan drug designation status are based on the first category, i.e., prevalence.¹³ In fact, by the end of 2017, only one application had been received under the ‘insufficient return on investment criterion’, and that was subsequently withdrawn.¹⁴

With a view to ensure that the pharmaceutical industry invests sufficient funds in the treatment of rare diseases, for which a sufficient financial return is not guaranteed, the Orphan Drug Regulation¹⁵ has introduced an incentive in the form of a stand-alone period of 10 years of market protection (or market exclusivity, both being the same thing).¹⁶ An additional 2 years of market exclusivity can be obtained in case of a paediatric use.¹⁷ Other incentives which the Orphan Drug Regulation provides, but which are beyond the scope of this article are access to the centralised procedure at EMA,¹⁸ possible fee reductions,¹⁹ and incentives to invest in R&D for orphan diseases, in particular to SME’s.²⁰ As said, we will limit ourselves to the ten years market exclusivity.



2.2 How the system works

In Europe, orphan medicinal products (OMPs) are designated by the European Commission on receipt of a positive opinion from the selected regulatory body – the Committee for Orphan Medicinal Products (COMP) – via a process commonly known as orphan drug designation (ODD). ODD can be granted at any stage in the medicine’s development. Opinions for designations are based on the following criteria:²¹

- The rarity of the condition (affecting no more than five in 10,000 people in the EU) or evidence of insufficient return in investment
- Seriousness of the disease/condition
- The existence of alternative methods of prevention, diagnosis or treatment (the EU stipulates that this should be a novel form of therapy for the condition; however, if there is an existing form of therapy, the orphan product must be of significant benefit to the patients and must have an advantage over existing therapies).²²

[2017] Orphanet Journal of Rare Diseases, 12:64.

¹¹ COMMISSION STAFF WORKING DOCUMENT, 2020, p.12.

¹² Is further defined in Art. 3(2) Regulation [EC] No 847/2000 of 27 April 2000 laying down the provisions for implementation of the criteria for designation of a medicinal product as an orphan medicinal product and definitions of the concepts ‘similar medicinal product’ and ‘clinical superiority’ as: “a clinically relevant advantage or a major contribution to patient care.”

¹³ A. DENIS, L. MERGAERT, C. FOSTIER, I. CLEEMPUT, S. SIMOENS, ‘Issues Surrounding Orphan Disease and Orphan Drug Policies in Europe’, [2010] Appl Health Econ Health Policy; 8 (5): [343-350] 345.

¹⁴ COMMISSION STAFF WORKING DOCUMENT,

2020, p.43.

¹⁵ REGULATION (EC) No 141/2000 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 December 1999 on orphan medicinal products, OJ 22.01.2000, L 18/1.

¹⁶ Art. 8 Regulation 141/2000.

¹⁷ Which is not compatible, however, with filing for a paediatric extension of a SPC. The applicant has to choose between going for a two additional year market protection for an orphan drug for paediatric use, or go for a one-off 6 months paediatric extension of an existing SPC, provided a Paediatric Investigation Plan (PIP) has been approved. See, Art. 36(4) of Regulation [EC] No 1901/2006 on medicinal products for paediatric use and amending Regulation [EEC] No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation [EC] No 726/2004.

See also Art. 13(3) Regulation 469/2009.

¹⁸ Art. 7 Regulation 141/2000.

¹⁹ Art. 7 Regulation 141/2000.

²⁰ Art. 9 Regulation 141/2000.

²¹ See Regulation [EC] No 847/2000 of 27 April 2000 laying down the provisions for implementation of the criteria for designation of a medicinal product as an orphan medicinal product and definitions of the concepts ‘similar medicinal product’ and ‘clinical superiority’.

²² See for this, R. OGBAH, ‘Orphan medicinal products – A European process overview’ [2015] 12/2 Regulatory Rapporteur, 5-11, at 5.



The procedure relating to orphan medicinal products consists of two separate phases:²³

1. designation – this can take place at any stage of development prior to the submission of a marketing authorisation application, provided that the sponsor can establish that the criteria in Article 3 of the Regulation are met. Designation has no effect on parallel developments by different sponsors. It is a tool to identify candidate products in a transparent way and to make them eligible for financial incentives. Designation will be confirmed by a separate Commission decision for each candidate product and the designated product will be entered in the Community Register for Orphan Medicinal Products (Article 5 of the Regulation);

and

2. marketing authorisation (MA).
The statistics demonstrate that the very large majority of orphan drug designations never makes it to an MA. Between 2000 and 2017, 1956 designations were granted and 142 orphan medicines were authorised (11 were subsequently withdrawn, thus leaving 131 on the market).²⁴ The most important regulatory exclusivity, i.e., the 10 years market exclusivity is only available for those orphan drug products that obtain an MA.

There have been critical observations as to whether the orphan drug system fulfils its promise. A rather large share is for anti-cancer treatments, followed by treatments for conditions of the alimentary tract and metabolic disorders.²⁵ As was established in the 2018 Report I co-authored, for quite a few of orphan diseases in general and even

more so for paediatric orphan diseases, the incentive system has not led to any meaningful uptake in drug development.²⁶ That is a first concern. However interesting and relevant this is, it is not the central focus of the present article, and will remain further undiscussed.

2.3 The exclusivity periods

As said, as an incentive reward to bring to market drugs for rare diseases, the orphan drug Regulation provides a “prize” of 10 years of market protection. Talking about that market exclusivity, we need to make a couple of important observations.

First, it must be emphasised, that the provision is worded in a somewhat peculiar manner, suggesting the 10 years exclusivity in fact to be a kind of hybrid of data and market protection. Indeed, the text of the relevant provision states that “the [European Union] and the Member States **shall not, for a period of 10 years, accept another application for a marketing authorisation**, or grant a marketing authorisation or accept an application to extend an existing marketing authorisation, for the same therapeutic indication, in respect of a similar medicinal product” (emphasis added).²⁷ Data exclusivity is there to prevent generics to file for a MA (in which the generic refers to the file of the reference product which has already been authorised). Market protection does not prevent generic versions of the reference product being filed, but it merely prevents generics from entering the market during the market protection period.

The wording of the orphan drug market protection suggests that an application cannot be accepted during the 10 years of market protection, which implies that generics can only file at the end of the 10 years market protection period, which gives a de facto longer period of market protection, as obtaining a MA for a generic version of an orphan drug after filing date can take around 1.5 years. This issue has mostly been overlooked in the literature, but it is worth noting, as it puts generic manufacturers in a competitive disadvantage compared to “regular” medicinal products (where they can file for a generic MA after the 8 years data exclusivity, so as to enter the market on day 1 after the end of the 10 years market exclusivity period).

Another important feature is that, unlike for “regular” medicinal products,²⁸ there are ways how multiple cumulative market protection periods can be obtained for similar orphan medicinal products.²⁹ One of the options is laid down in Art. 8(3) Regulation 141/2000:

“3. By way of derogation from paragraph 1, and without prejudice to intellectual property law or any other provision of [EU] law, a marketing authorisation may be granted, for the same therapeutic indication, to a similar medicinal product if: (a) the holder of the marketing authorisation for the original orphan medicinal product has given his consent to the second applicant, or (b) the holder of the marketing authorisation for the original orphan medicinal product is unable to supply sufficient quantities of the medicinal product, or (c) the second applicant can establish in the application that the second medicinal pro-

duct, although similar to the orphan medicinal product already authorised, is safer, more effective or otherwise clinically superior.”³⁰

The above describes the situation that similar orphan medicinal products can benefit from multiple market exclusivity periods, provided that the conditions under Art. 8(3) Regulation 141/2000 are being met. One such option would be that the first MA holder grants consent to a second MA holder for a similar medicinal product for the same therapeutic indication. It is hence also possible to accumulate market exclusivity periods for the same therapeutic indications.

But another option to accumulate market exclusivity periods is under the scenario that the same active substance becomes the subject of multiple orphan drug designations, and to the extent that two or more of those orphan drug designations lead to a MA, the same active substance will lead to multiple MA's (for different therapeutic indications), and for each of those MA's, a separate

10 years exclusivity period is triggered. That also allows to accumulate market exclusivities. Take for instance active substance A for orphan drug indication X, for which an MA is obtained on 1 May 2005. If for that same substance A another orphan drug indication Y is found, and if that leads to another MA, for instance on 1 October 2010, that second MA will trigger its own 10 years exclusivity period. That means that active substance A for orphan drug indication X will benefit from market exclusivity until 1 May 2015, and that same active substance A for orphan drug indication Y will benefit from 10 years market exclusivity until 1 October 2020. It is not uncommon that in such a scenario, the orphan drugs indications for which the multiple MA's have been granted overlap, which de facto extends to a potentially longer than 10 years period of some form of exclusivity in active substance A. In our example market exclusivity on the active substance in some form will extend from 2005 to 2020 (see also Figure 1 for a graphic representation).

²³ Case T-74/08, *Novo Pharm AG v European Commission*, ECLI: EU:T:2010:376, paragraph 33.

²⁴ COMMISSION STAFF WORKING DOCUMENT, 2020, p.35.

²⁵ COMMISSION STAFF WORKING DOCUMENT, 2020, p.24.

²⁶ T. DE JONG, A. RADAUER, S.J.R. BOSTYN, J. POORT, 'Effects of Supplementary Protection Mechanisms for Pharmaceutical Products', May 2018, Technopolis Group, 169 pp (hereinafter Technopolis Report 2018), downloadable at <https://www.technopolis-group.com/report/effects-of-supplementary-protection-mechanisms-for-pharmaceutical-products/>, p. 98-99.

²⁷ Art. 8 of Regulation No 141/2000, which reads in full: "1. Where a marketing authorisation in respect of an orphan medicinal product is granted pursuant to [Council] Regulation [EEC] No 2309/93 [of 22 July 1993 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products [OJ 1993 L 241, p. 1]] or where all the Member States have granted marketing authorisations in accordance with the procedures for mutual recognition laid down in Articles 7 and 7a of Directive 65/65/EEC or Article 9(4) of Council Directive 75/319/EEC of 20 May 1975 on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products [OJ 1975 L 147, p. 13], and without prejudice to intellectual property law or any other provision of [EU] law, the [European Union] and the Member States shall not, for a

period of 10 years, accept another application for a marketing authorisation, or grant a marketing authorisation or accept an application to extend an existing marketing authorisation, for the same therapeutic indication, in respect of a similar medicinal product."

²⁸ For "regular" medicinal products, the so-called GMA, discussed further below, would prevent that.

²⁹ Art. 3(3)(b) Regulation (EC) No 847/2000 defines "similar medicinal product" as a "medicinal product containing a similar active substance of substances as contained in a currently authorised orphan medicinal product, and which is intended for the same therapeutic indication." The concept of "similar active substance" is in turn defined in the same Art. 3 sub 3(c) as: "an identical active substance, or an active substance with the same principal molecular structural features (but not necessarily all of the same molecular structural features) and which acts via the same mechanism." It includes in any event isomers, mixture of isomers, complexes, esters, salts and non-covalent derivatives of the original active substance, or an active substance that differs from the original active substance only with respect to minor changes in the molecular structure, such as a structural analogue.

³⁰ Is further defined in Art. 3(3)(d) Regulation (EC) No 847/2000 of 27 April 2000 laying down the provisions for implementation of the criteria for designation of a medicinal product as an orphan medicinal product and definitions of the concepts 'similar medicinal product' and 'clinical superiority': "'clinically superior' means that a medicinal product is

shown to provide a significant therapeutic or diagnostic advantage over and above that provided by an authorised orphan medicinal product in one or more of the following ways:

- (1) greater efficacy than an authorised orphan medicinal product (as assessed by effect on a clinically meaningful endpoint in adequate and well controlled clinical trials). Generally, this would represent the same kind of evidence needed to support a comparative efficacy claim for two different medicinal products. Direct comparative clinical trials are generally necessary, however comparisons based on other endpoints, including surrogate endpoints may be used. In any case, the methodological approach should be justified;

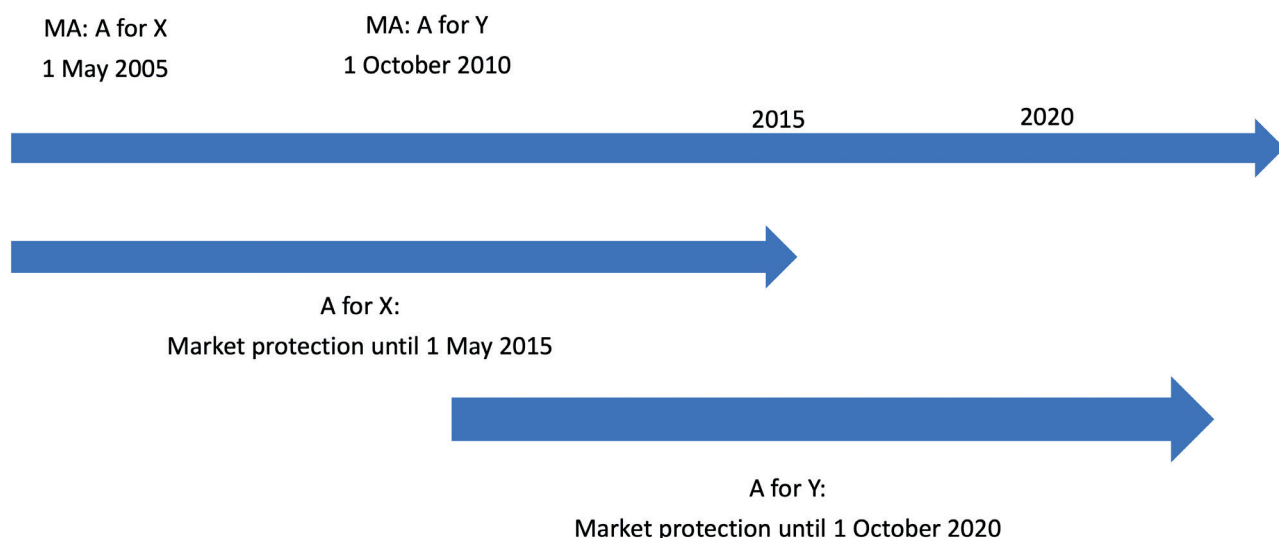
or

- (2) greater safety in a substantial portion of the target population(s). In some cases direct comparative clinical trials will be necessary;

or

- (3) in exceptional cases, where neither greater safety nor greater efficacy has been shown, a demonstration that the medicinal product otherwise makes a major contribution to diagnosis or to patient care."

Figure 1:



The above is possible for orphan drugs because of the absence of the so-called Global Marketing Authorisation (GMA) concept for orphan drugs. That means that the same active substance can obtain multiple orphan drug designations, and for each of those that leads to an orphan drug MA, a separate 10 years market exclusivity is triggered.

The concept of “global marketing authorisation” is a crucial one for “regular” drugs as it is the trigger of the regulatory exclusive rights which are the subject of this article. **Once a medicinal product has been authorised, any additional strengths, pharmaceutical forms, administration routes, presentations, as well as any variations and extensions which could become authorised in the future will all fall within the same global marketing authorisation and cannot trigger a separate entitlement to regulatory exclusivity, such data and market exclusivity. All these variations and extensions will not be entitled to their own data and market exclusivity, at least in principle.**³¹ Thus, the GMA contains the initial authorisation and all of the above-mentioned variations. In other words, as long as the product is held to be the “same” active substance, all changes to that active substance as laid out above cannot trigger a separate period of regulatory exclusivity, but all fall within the same GMA. That is of course important, as drug developers must take into account that any such changes will not benefit from additional regulatory exclusivity protection, apart from the rather limited cases set out above. There are a limited number of exceptions, where a 1 year extension can be obtained.³²

This is different from patent law, for instance, where different salts, pharmaceutical forms or administration routes could be protected separately by patents, provided that they are found novel, inventive and sufficiently

disclosed. The regulatory system is not that generous in the context of regulatory exclusivity protection. That probably also explains why pharmaceutical companies have been focussing so heavily on obtaining patent protection, absent any other means of obtaining exclusivity in the regulatory framework.

A good illustration of the issues is case C-629/15,³³ where the issue was whether Novartis could invoke data exclusivity protection for a MA obtained for Aclasta, which had zoledronic acid as the active substance, for specific medical indications, whilst there was an earlier MA for Zometa, also having the active substance zoledronic acid but for different medical indications. The generic pharmaceutical companies referred to Aclasta as the reference product in this case, and Novartis claimed that, as the companies filed to register the active substance for medical indications falling under the Aclasta product, it was entitled to a separate period of data and market exclusivity for Aclasta, which, in case Aclasta would have generated a new period of data and market exclusivity, it would not have lapsed at the time of filing for MA’s by the generic pharmaceutical companies.

By the decisions at issue, the Commission granted MAs for Z.a. Teva and for Z.a. Hospira.³⁴ Novartis appealed the decision to grant a MA for Z.a. Teva and for Z.a. Hospira, arguing that this was an infringement to Art. 10(1) Directive 2001/83. It claimed that it was entitled to data exclusivity for 10 years based on the MA for Aclasta. It was claimed in this case that a MA for specific medical indications relating to an active substance that had already been subject to a MA for different medical indications earlier did not fall under the same “GMA” generated for the first MA, and that the MA holder for the later medical indications was hence entitled to a new period of data and market exclusivity for the later MA for the medical indications.

The CJEU did not follow this reasoning and held that the MA for the further medical indications of the active substance could not generate a new “GMA” and hence entitlement to a fresh period of data and market exclusivity, but that those further indications all fell within the scope of the “GMA” already generated by the MA for the active substance earlier, even if this was for different medical indications.

The case arrived at the CJEU after an appeal by Novartis against the judgements of the General Court in this case.³⁵ The CJEU confirmed the reasoning of the General Court and held that all the different medical indications and strengths of zoledronic acid, which in the case of Novartis, had been the subject of two different MA’s, belong to the same GMA and can consequently not lead to two separate periods of data and market exclusivity, but fall all within the same period of data and market exclusivity.

As said, it has been decided not to make the concept of GMA applicable to orphan drugs, so as to make the incentive more attractive. Indeed, the existence of a GMA concept for orphan drugs would largely prevent accumulation of market exclusivities, whilst its absence allows accumulation of the same, as we will see in more detail in what follows.

The fact that multiple market exclusivities can be granted for the same active substance, be it for different orphan drug indications, can pose problems for generic entry. If the product (for instance the “pill” formulation) on the market as an orphan drug product is still under market exclusivity, no generic entry can take place. In principle, for each of the orphan drug indications for which there is no longer orphan drug market exclusivity, generic entry is possible. However, if it is the same active substance in the same formulation, this might very well lead to infringement issues. Using the example I laid out earlier, if gene-

ric orphan drug A is on the market for indication X that is no longer under market exclusivity, but it can also be used in a cross-label fashion for indication Y which is still under market exclusivity,³⁶ this could lead to infringement problems, and might de facto delay generic entry. I will explain this more in detail in what follows, and it also brings us to the issues of sub-setting and indication stacking.

Cross-label use is the practice where a physician prescribes a generic version of an innovator drug that has been authorised for the protected use. In other words, the physician prescribes a generic drug, which in itself is not authorised for a specific orphan drug use under protected, but the it is a drug which is bioequivalent to an innovator drug which benefits still from market exclusivity for an orphan drug use. The situation is especially prevalent in situations of repurposing of drugs, i.e., the situation where an existing drug benefits from market exclusivity for a new orphan drug use. As the active substance is already on the market, and indeed generic entry is legally allowed for certain uses (and provided the formulation of the active substance remains substantially the same), it is quite common for physicians to prescribe that generic version for a use which still benefits from (orphan) drug exclusivity. It is common for both “regular” drugs and orphan drugs. The major difference is that, as “regular” drugs use the GMA concept, repurposing is largely unrewarded under regulatory exclusivities (apart from a once 1 year extension in specific cases). Cross-label prescription will consequently not have any fundamental consequences under the regulatory exclusivity regime for regular drugs (but it has for patent protection though).³⁷ For orphan drugs, the situation is quite different indeed. As orphan drugs do not use the GMA concept, the accumulation of exclusivities does present potential problems regarding infringement and regulatory exclusivities.

³¹ Article 6(1) second subparagraph of Directive 2001/83/EC, of the European Parliament and of the Council of Nov. 6, 2001 on the Community Code Relating to Medicinal Products for Human Use (hereinafter Directive 2001/83/EC): “When a medicinal product has been granted an initial marketing authorisation in accordance with the first sub-paragraph, any additional strengths, pharmaceutical forms, administration routes, presentations, as well as any variations and extensions shall also be granted an authorisation in accordance with the first sub-paragraph or be included in the initial marketing authorisation. All these marketing authorisations shall be considered as belonging to the same global marketing authorisation, in particular for the purpose of the application of Article 10(1).”

³² One year extension of the 10 year period in Article 10(1) in the case of new therapeutic indications which, during the scientific

evaluation prior to their authorisation, are held to bring a significant clinical benefit in comparison with existing therapies [Art. 10(4) Directive 2001/83; Art. 14(11) of Regulation (EC) No 726/2004]; One year period of data protection for new indications of well-established substances [Article 10(5) of Directive 2001/83/EC. For a definition of well-established substance and use, see Part II of the Annex to Directive 2001/83/EC as amended by Directive 2003/63/EC]; One year period of protection for data supporting a change of classification [Article 74a of Directive 2001/83/EC, introduced by Directive 2004/27/EC].

³³ C-629/15, *Novartis Europharm Ltd v. European Commission*, ECLI:EU:C:2017:498.

³⁴ *Ibidem*, para 15-20.

³⁵ *Novartis Europharm v. Commission* [T-472/12, EU:T:2015:637], and *Novartis Europharm v. Commission* [T-67/13, not published, EU:T:2015:636].

³⁶ This is by no means a theoretical scenario. Cross-label use is frequently done, also with a view to save costs for public health care systems. Moreover, there is also evidence that off-label use in the paediatric environment is even more rampant: “Depending on the therapeutic area concerned, between 50% and 90% (for example, cancer treatments and HIV treatments) of authorised medicines in the EU were used off-label in children, i.e.. without their effects on children having been studied.” See, COMMISSION STAFF WORKING DOCUMENT, 2020, p.20.

³⁷ For more details on cross-label prescription and patent infringement problems, see, S.J.R. BOSTYN, ‘Personalised medicine, medical indication patents and patent infringement: emergency treatment required’, [2016] *Intellectual Property Quarterly*, 151-201 (hereinafter BOSTYN, IPQ, 2016a).

3 SUB-SETTING (SALAMI SLICING), INDICATION STACKING AND DELAY TO GENERIC ENTRY

It is in the context of generic entry delay that I want to discuss two specific features which are made possible under the orphan drug system in Europe, i.e., sub-setting and indication stacking.

Indeed, it has been pointed out in the literature³⁸ that, although the system of orphan designation is designed to grant orphan status to an appropriate drug, the current system can be (mis)used to artificially create orphan drugs or orphan diseases.³⁹ This can happen when drugs are developed for a specific type of patient/disease (a practice called ‘targeting’), or when one disease is split into various subcategories, each of which exhibits its own characteristics (a practice called “sub-setting”).⁴⁰ Sub-setting can lead to so-called “salami-slicing”, where artificial subsets of a non-orphan disease are created, with a view to qualify as several orphan diseases.⁴¹ Indeed, the phenomenon of salami-slicing refers to splitting certain common diseases into many ‘artificial’ subsets. Each of these subsets could then be considered a rare disease (such as certain forms of cancer). Under the EU Regulation it is possible to obtain orphan designations for subsets of common diseases (although only subject to stringent conditions).

At the same time, advances in personalised medicine may add another layer of complexity to the current regulatory framework. Such developments may hold great potential for optimal tailoring of treatments to diseases and patients. However, they should not lead to unnecessary multiplications of rare diseases out of common diseases, to gain market exclusivity periods.⁴² Especially in the field of oncology, we cannot but think that this is a practice that takes place there. There are of course many different genetic mutations one can identify, and on that basis, a new sub-set can be identified. In my view, that is a field that requires more attention than it receives today.

Another practice, which we have already discussed with the example we used above is indication-stacking. There are currently 22 orphan products authorised for two or more orphan indications on the EU market. These indications refer to distinct orphan conditions, and each

entitles the product in question to a period of market exclusivity. These periods may run in parallel, with their own start and finish dates.⁴³ If a product receives an authorisation for an additional indication or indications, it is assigned a new period of exclusivity for that specific indication. For the reasons we have explained above, this may present issues for generic market entry, as the web of different indications and orphan drug products with those overlapping indications on the market can present obstacles for generic entry. That is even more the case if the generic products could be prescribed cross-label for indications which are still under market exclusivity.

Sub-setting and indication stacking have led to complex strategies used by pharmaceutical companies to optimise exclusivity and delay generic entry. Let us analyse a couple of examples to see how these strategies have played out.

The orphan drug Revlimid[®] was approved for the treatment of multiple myeloma, myelodysplastic syndromes and mantle cell lymphoma, subject to certain conditions regarding the patient’s previous treatment. Revlimid[®] contains the active ingredient Lenalidomide and is developed and marketed by Celgene. The exclusivity covers a combination of patent and SPC protection, and multiple MA’s, covering different orphan drug indications, each leading to a separate period of 10 years orphan drugs market exclusivity.

Revlimid[®]⁴⁴ obtained patent protection in 1997 and different MA’s for orphan drug indications. The patent expired on 27 July 2017, and the SPC expired on 18 June 2022. A follow-up patent for the polymorph form of Lenalidomide got invalidated and is no longer relevant.

The following orphan drug designations and MA’s have been granted for Revlimid[®] in Europe (each accompanied)

- Orphan market exclusivity for “Treatment of multiple myeloma” (designation EU/3/03/177) started on 19/06/2007 and ended on 19/06/2017.
- Orphan market exclusivity for “Treatment of myelodysplastic syndromes” (designation EU/3/04/192) started on 17/06/2013 and will expire on 17/06/2023.
- Orphan market exclusivity for “Treatment of mantle cell lymphoma” (designation EU/3/11/924) started on 12/07/2016 and will expire on 12/07/2026.

³⁸ A. DENIS, L. MERGAERT, C. FOSTIER, I. CLEEMPUT, S. SIMOENS, ‘Issues Surrounding Orphan Disease and Orphan Drug Policies in Europe’, [2010] *Appl Health Econ Health Policy*, 8 (5): [343-350] 344.

³⁹ W. YIN, ‘R&D policy, agency costs and innovation in personalized medicine’ [2009] *J. Health Econ.*, 28: 950-62.

⁴⁰ European Medicines Agency. COMP report to the Commission in relation to article 10 of regulation 141/2000 on orphan medicinal products. London: European Medicines Agency, 2007.

⁴¹ Technopolis Report 2018, p. 102.

⁴² COMMISSION STAFF WORKING DOCUMENT, 2020, p.68.

⁴³ COMMISSION STAFF WORKING DOCUMENT, 2020, p.68.

⁴⁴ Figure 2 represents the sequence of events in a timeline.

⁴⁵ Taken from paragraphs 9-14 of C-138/15 P, *Teva Pharma BV and Teva Pharmaceuticals Europe BV v. European Medicines Agency (EMA)*, ECLI:EU:C:2016:136.

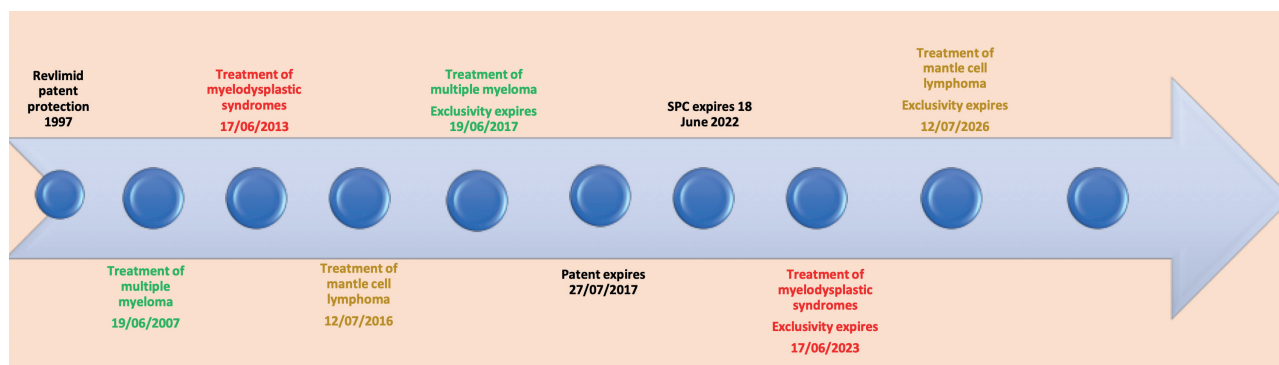
⁴⁶ Using the calculation formula laid down in Art. 13 Regulation (EC) No 469/2009 of the

European Parliament and of the Council of 6 May 2009 concerning the supplementary protection certificate for medicinal products (OJ L 152, 16.6.2009, p. 1–10).

⁴⁷ Art. 36(1) of Regulation (EC) No 1901/2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004. See also Art. 13(3) Regulation 469/2009.

⁴⁸ See Art.36 Regulation 1901/2006 (Paediatric Regulation).

Figure 2:



As can be seen from the above, there are multiple MA's for orphan drug indications, and each of those generates a separate ten years market exclusivity period (and the last orphan drug MA being granted in 2016). Consequently, market exclusivity for the drug will end in 2026, four years after the SPC based on the basic patent filed in 1997 has lapsed. This shows that a combination of patent and SPC protection, and a very strategic use of the possibility to accumulate market exclusivities for new orphan drug MA's allows to extend exclusivity protection from 1997 to 2026 (which is almost 30 years from the filing date of the basic patent, being the first exclusivity date for the drug).

A second example is Glivec. On 7 November 2001, the Commission granted Novartis a marketing authorisation for imatinib under the commercial name Glivec for the treatment of adult patients with CML in chronic phase after failure of interferon-alpha therapy, or in accelerated phase or blast crisis. Subsequently, the Commission extended the terms of that marketing authorisation to cover other orphan conditions. Pursuant to Article 8 of Regulation No 141/2000, the period of exclusivity enjoyed by Glivec expired on 12 November 2011.

On 22 May 2006, the Commission designated and registered as an orphan medicinal product nilotinib, a medicinal product for the treatment of CML, which was sold under the commercial name Tasigna and developed by the holder of the marketing authorisation for Glivec. In the course of the marketing authorisation procedure for Tasigna, that holder indicated to the EMA that it consented to authorisation being granted for the marketing of that similar medicinal product for the same therapeutic indications as those covered by the marketing authorisation granted for Glivec, in accordance with Article 8(3)(a) of Regulation No 141/2000. On 19 November 2007, the Commission adopted a decision authorising the marketing of Tasigna for the treatment of adult patients with CML in chronic phase and accelerated phase, with resistance or intolerance to prior treatment involving Glivec. On 20 December 2010, the Commission extended the terms of that marketing authorisation to cover the treat-

ment of adult patients with newly diagnosed CML in chronic phase.

On 5 January 2012, Teva Pharmaceuticals Europe BV applied on behalf of Teva Pharma BV for authorisation to place on the market a generic version of Glivec. That application referred, inter alia, to certain CML therapeutic indications covered by the marketing authorisation granted for Tasigna.

The EMA refused to grant that application, in so far as it covered the CML therapeutic indications for which Tasigna enjoyed marketing authorisation, on the ground that those therapeutic indications still enjoyed market exclusivity protection under Article 8(1) of Regulation No 141/2000.⁴⁵

Imatinib had been patented by Novartis in 1993. Taken that the first MA was granted in November 2001, the SPC for the patent lapsed in 2016,⁴⁶ and there was an entitlement to a one-off six months SPC extension based on an approved Paediatric Investigation Plan (PIP).⁴⁷

Even though the market exclusivity for Glivec expired on 12 November 2011, the follow-up product Tasigna was still under market exclusivity at that time (which has lapsed in November 2017). Novartis withdrew Glivec product from the orphan register, however, in 2012. The reason for that was that it wanted to file for a six months paediatric extension of the SPC granted for the basic patent. Under the orphan drug system, it is not possible to file for a paediatric extension of an SPC for a patent.⁴⁸ Withdrawing Glivec from the orphan drug register could be done without much harm, as there was still market exclusivity for Tasigna until November 2017, and as a two years paediatric exclusivity was also obtained, until November 2019. In doing so, Novartis could kill two birds with one stone. It was capable of obtaining six months SPC extension based on its basic patent, whilst at the same time still retaining orphan drug market exclusivity for a similar medicinal product, i.e., Tasigna, for overlapping medical indications. This strategy optimised its exclusive rights position, delaying generic entry.

An overview of the various MA's and market exclusivity periods can be found below:

Glivec, Imatinib (MA number EU/1/01/198):

- Orphan market exclusivity for "Treatment of chronic myeloid leukaemia" (based on designation EU/3/01/021) started on 12/11/2001. This orphan market exclusivity has ended on 12/11/2011
- Orphan market exclusivity for "Treatment of malignant gastrointestinal stromal tumours" (based on designation EU/3/01/061) started on 27/05/2002. This orphan market exclusivity has ended on 16/04/2012 (withdrawal of orphan drug status).
- Orphan market exclusivity for "Treatment of acute lymphoblastic leukaemia" (based on designation EU/3/05/304) started on 18/09/2006. This orphan market exclusivity has ended on 16/04/2012 (withdrawal of orphan drug status).
- Orphan market exclusivity for "Treatment of dermatofibrosarcoma protuberans" (based on designation EU/3/05/305) started on 18/09/2006. This orphan market exclusivity has ended on 16/04/2012 (withdrawal of orphan drug status).
- Orphan market exclusivity for "Treatment of chronic eosinophilic leukaemia and the hypereosinophilic syndrome" (based on designation EU/3/05/320) started on 01/12/2006. This orphan market exclusivity has ended on 16/04/2012 (withdrawal of orphan drug status).
- Orphan market exclusivity for "Treatment of myelodysplastic/myeloproliferative diseases" (based on designation EU/3/05/340) started on 01/12/2006. This orphan market exclusivity has ended on 16/04/2012 (withdrawal of orphan drug status).

Tasigna, Nilotinib (MA number EU/1/07/422):

- Orphan market exclusivity for "Treatment of chronic myeloid leukaemia" (based on designation EU/3/06/375) started on 21/11/2007. This orphan market exclusivity expired on 21/11/2017. An additional two years paediatric market exclusivity was obtained, which expired on 21/11/2019.

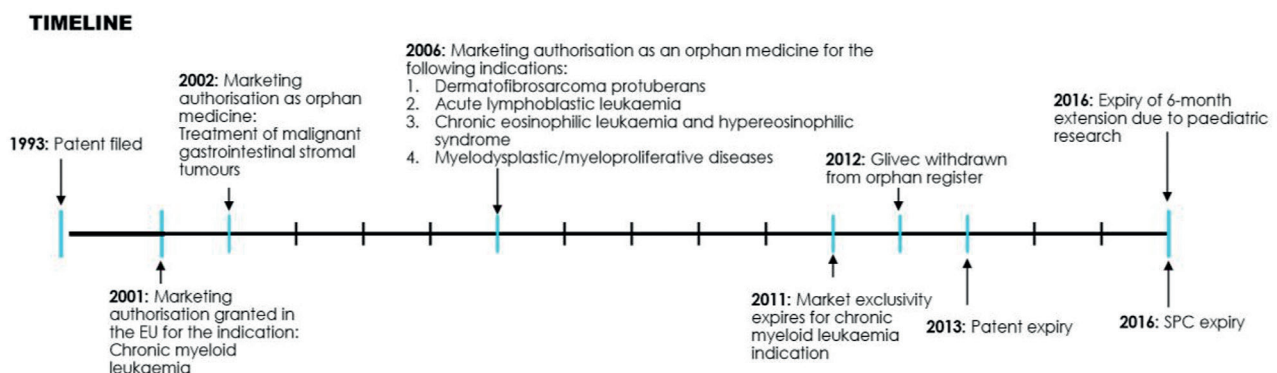
Figure 3:⁴⁹

For Imatinib, Novartis would have been entitled to marketing exclusivity until 16 April 2016 (with a first MA date on 12 November 2001, which would have implied an almost 15 year exclusivity period. It withdrew the orphan drug status for Imatinib as it had a follow-up product, Tasigna, which still benefitted from exclusivity protection until 2019 (including the market exclusivity paediatric extension of 2 years). In other words, they could invoke Tasigna against generic entry in respect of marketing exclusivity for the active substance, whilst they could focus for Imatinib on the SPC paediatric extension (which is not compatible with the orphan drug paediatric extension).

What the above examples demonstrate is that pharmaceutical companies go at extreme lengths to optimise exclusivity protection on the products they put on the market. That could be achieved by taking advantage of the accumulation of exclusivities which the orphan drug system allows, but also by strategizing which combination of exclusive rights provides them the best position. That could be achieved by dropping certain exclusivities if they would not be compatible with other exclusive rights (such as orphan drug paediatric exclusivity extension being incompatible with obtaining a six months paediatric SPC extension) whilst at the same time ensuring that there are follow-on overlapping products that still provide the maximum exclusivity protection under regimes which would otherwise be mutually incompatible within the same medicinal product. It could be argued that this has very little to do with using incentive mechanisms to bring much needed new products on the market, but more with optimising revenues and delaying generic entry.

It should be equally clear from the above examples that it is not difficult to imagine examples where sub-setting, combined with indication stacking where relevant, could be an appealing strategy to delay generic entry, because of the fact that market exclusivity periods could be accumulated.

Figure 3:



4 SUGGESTIONS FOR THE FUTURE

4.1 The problems

Sub-setting and indication stacking allow the accumulation of market exclusivities, and can delay generic entry, as the examples above have shown.

Some, however, have argued that there is no real problem with the accumulation of market exclusivities, as each exclusivity follows the other, and the orphan drug for which the market exclusivity has lapsed becomes available for generic entry at no risk. Indeed, the argument is often used that the potential harm done by cumulative MA's for different orphan indications (which comes with each of their own ten years orphan drug market exclusivity) is limited, as after the market exclusivity for each of the orphan drug MA's has lapsed, generics can enter the market with generic versions of the drug for those indications which are no longer under market exclusivity.⁵⁰

This line of argumentation is in my view ill-conceived, and is likely inspired by a lack of expertise in other areas of exclusive rights for pharmaceuticals. That argument overlooks the fact that generics can continue to be hampered if the drug formulation remains the same for each of those different orphan indications. If that is the case, physicians may prescribe the generic version of the orphan drug cross-label (or even off-label) for those indications which are still under market exclusivity. That can and will lead to scenarios very similar to the ones we see in the context of second medical use patents, which I will need to briefly address in what follows.

The drafters of the European Patent Convention (EPC) did not allow for patent protection for medical treatment methods,⁵¹ as this was deemed to be not in conformity with societal views that physicians should not be hindered by patents when they chose or carried out a treatment method⁵² (or diagnostic method on the human body or



surgical method for that matter).⁵³ Pharmaceutical products and medical instruments were on the other hand perfectly deemed patentable.

They did, however, provide for the protection of medical uses of an existing pharmaceutical compound,⁵⁴ thereby creating an exception to the strict novelty requirement under patent law.⁵⁵ Indeed, a first basic principle of patent law is that one can patent a new chemical entity as such as long as it does not form part of the state of the art. The drafters only provided for patent protection for the first medical use of an existing compound in the wording of the 1973 version of the EPC.⁵⁶ Under the literal wording of the EPC 1973, it was possible to obtain purpose limited product protection for the first medical use of an already existing drug. Such patent claim would typically read as “product X for the use as a medicament”. It will immediately be understood that this is a very wide claim indeed, covering ALL medical applications of a known substance.⁵⁷ As a matter of practice, in virtually all cases, the claim is part of the patent which claims the chemical entity as such.

⁴⁹ Figure 3 is taken from the COMMISSION STAFF WORKING DOCUMENT, 2020, p 69.

⁵⁰ See COMMISSION STAFF WORKING DOCUMENT, 2020, p.68: “While overlapping or consecutive periods of market exclusivity can delay generic entry and may block the development of generic orphan medicines, they cannot prevent generic entry altogether, as each exclusivity period is tied to a specific orphan indication. A manufacturer willing to produce and market a generic version of an orphan medicine once the first market exclusivity period has expired is entitled to do so.”

⁵¹ In the US, medical treatment methods are perfectly patentable.

⁵² See G 2/08, Dosage regime/ABBOTT RESPIRATORY, OJ EPO, 2010, 456, reasons 5.3.

⁵³ Art. 52(4) EPC 1973, Art. 53(c) EPC 2000: Article 53(c) EPC2000: “European patents shall not be granted in respect of: [...]c) methods for treatment of the human or animal body by surgery or therapy and diagnostic methods practised on the human

or animal body; this provision shall not apply to products, in particular substances or compositions, for use in any of these methods.” For more details, see, S.J.R. BOSTYN, ‘Medical treatment methods, medical indication claims and patentability: A quest into the rationale of the exclusion and patentability in the context of the future of personalised medicine’, [2016] IPQ, 203-230, [hereinafter BOSTYN, IPQ, 2016b].

⁵⁴ For more details, see, BOSTYN, IPQ, 2016a; E. VENTOSE, Medical Patent Law – The Challenges of Medical Treatment (Edward Elgar Publishing, Cheltenham, 2011); F-E HUFNAGEL, ‘Der Schutzbereich von Second Medical Use Patente’ [2014] Gewerblicher Rechtsschutz und Urheberrecht (GRUR) 123-127; P. MEIER-BECK, ‘Patentschutz für die zweite medizinische Indikation und ärztliche Therapiefreiheit’, in, [2009] GRUR, 300-305; D. THUMS, ‘Patent Protection for Medical Treatment --A Distinction Between Patent and Medical Law’, [1996] International Review of Intellectual Property and Competition Law (IIC), 423 et seq.; H.

SCHACHT, Therapiefreiheit und Patentschutz für die weitere medizinische Indikation, (Nomos Verlagsgesellschaft, Baden-Baden, 2014); E.-M., MUELLER, Die Patentfähigkeit von Arzneimitteln. Der gewerbliche Rechtsschutz für pharmazeutische, medizinische und biotechnologische Erfindungen (Springer-Verlag, Berlin Heidelberg, 2003).

⁵⁵ See Art. 54 EPC.

⁵⁶ Article 54(5) EPC1973 reads: “The provisions of paragraphs 1 to 4 shall not exclude the patentability of any substance or composition, comprised in the state of the art, for use in a method referred to in Article 52, paragraph 4, provided that its use for any method referred to in that paragraph is not comprised in the state of the art.” Under the EPC2000, the almost identical provision is now in Article 54(4).”

⁵⁷ SCHACHT has probably rightly so criticised the very broad scope of those first medical indication claims, see, H. SCHACHT, *op.cit.*, p. 260-267.



What now if there was a situation where one invented yet another medical indication of an existing drug, for instance assume that someone invents that a drug can be used for the treatment of a certain condition? And what about the situation where another party (or for that matter the same party) invents yet another use of that same substance, for instance that the drug can be used for the treatment of yet another condition?⁵⁸ There was nothing in the statute about that eventuality.

Very quickly after the EPC entered into force, pharmaceutical companies argued that absent protection for further medical uses of an already patented or known substance, innovation into and development of medicinal products would be stifled, arguing that research into developing these new applications of existing drugs was expensive and laborious and deserved to be shielded from immediate copying by competitors if this type of research which was claimed to be of much benefit to society were to be continued. Whether that was a wise decision is not a matter for this article.⁵⁹

Case law eventually provided a solution and allowed also claims for what was then called second and further medical indications. Absent a statutory provision under the EPC1973, case law had to be inventive, and came up

with what was then called the “Swiss claim” according to which one could protect “the use of a substance X for the manufacture of a medicament for the treatment of disease Y”.⁶⁰ The Enlarged Board of Appeal (EBA) came in the seminal G 5/83 case⁶¹ first to the conclusion that the EPC had not envisaged to exclude second and further medical indication patents, to devise then a claim formulation that would fit within the confines of the then EPC1973. As a Swiss claim formulation does not protect the product as such, it was allowable.

Most common types of second medical use patents cover those inventions relating to a novel group of subjects,⁶² subpopulations (at least in some jurisdictions),⁶³ relating to a new route or mode of administration,⁶⁴ relating to a different technical effect and leading to a truly new application,⁶⁵ and those relating to a new dosage regime for an existing drug.⁶⁶

At the occasion of the negotiation of a new EPC (now known as EPC2000), it was deemed useful to codify the patentability of second medical uses. A new provision was introduced to that effect, allowing now also product claims for second and further medical uses, as that would be in line with what was already in existence for the first medical use, and it would also allegedly do away with the complications which were experienced with the Swiss claims. This new provision hence specifically allowed purpose limited product claims for second and further medical indication claims, confusingly also in Art. 54(5) EPC2000 (the first medical indication claim principle now laid down in Article 54(4) EPC2000).⁶⁷ A typical claim under this new provision would read “product X for the use in the treatment of disease Y”. This type of claim is what is called a purpose limited product claim, i.e., it protects the product but the scope is limited to the specific purpose or function of the product as laid down in the patent.⁶⁸

Understanding some of those basic concepts of patenting pharmaceuticals is necessary to understand the next step in the reasoning, and that is the issue of enforcement of such medical indication patents.

What is the problem here? Imagine the following

⁵⁸ E.g., a drug that is used for the treatment of epilepsy, and it is later discovered and patented that that same substance can also be used for the treatment of pain.

⁵⁹ I have expressed some views on this in my, BOSTYN, IPQ, 2016a; BOSTYN, IPQ, 2016b.

⁶⁰ Reason for this rather complicated claim formula was that there were some stumbling blocks within the EPC that prevented the courts to come to a more elegant solution. In view of the fact that Article 54(5) EPC1973 only allowed to claim the first medical indication as a product, as we have seen above, a product claim was no longer possible. And according to Article 52(4) EPC1973, medical treatment methods could

equally not be patented. That had as a consequence that a claim covering the “use of a substance X for the treatment of disease Y” was equally not possible. A claim for the use of a substance is nothing more than a method claim, and the abovementioned claim would hence cover a medical treatment.

⁶¹ G 5/83, Second medical indication/EISAI, OJ EPO, 1985, 60.

⁶² T 19/86, OJ EPO 1989, 24; T 893/90 of 22 July 1993; T 233/96 of 4 May 2000.

⁶³ T 1399/04, Combination therapy HCV/SCHERING, decision de dato 25 October 2006; T 0734/12, Arthritis patients with an inadequate response to a TNF-alpha

inhibitor/GENENTECH, INC., decision de dato 17 May 2013.

⁶⁴ T 51/93 of 8 June 1994; T 138/95 of 12 October 1999.

⁶⁵ T 290/86, OJ EPO 1992, 414; T 254/93, OJ EPO 1998, 285; T 1020/03, OJ EPO 2007, 204.

⁶⁶ G 2/08, Dosage regime/ABBOTT RESPIRATORY, OJ EPO, 2010, 456.

⁶⁷ Art. 54(5) EPC: “Paragraphs 2 and 3 shall also not exclude the patentability of any substance or composition referred to in paragraph 4 for any specific use in a method referred to in Article 53(c), provided that such use is not comprised in the state of the art.”

⁶⁸ For more details on the distinction between absolute and purpose limited product

scenario. The pharmaceutical compound as such is no longer patent protected. That means that the compound can be lawfully put on the market by a generic company, absent any IP protection. Imagine now also that a patent for an earlier second medical indication for condition X is also no longer under patent protection, and is being supplied by one or more generic pharmaceutical companies. However, there is still patent protection for a further medical use of the same compound to treat condition Y. What now if a physician prescribes the generic drug for a patented medical use (in my example to treat condition Y), and the pharmacist dispenses the generic drug for that same patented use? Is there patent infringement and if so by whom? Even if the physician and the pharmacist might be infringers, the patent holder will have no immediate incentive to sue those for patent infringement. He might be more interested in suing the generic company. Without having the space to go into detail here, the conclusion is that the generic company is liable for infringement if it knows or should have reasonably known that at least some of the generic drugs he produces are going to be prescribed and dispensed for the use in a patented medical indication. In certain jurisdictions, a qualified foreseeability test is being applied, according to which the generic manufacturer would not be liable to damages if he can prove that he has taken all reasonable measures with a view to prevent that his generic products are being used for the patented medical indication. In others, liability could be limited to situations where the generic product is prepared and presented in a way that infringement is clear from the presentation.⁶⁹

The case law is rather unclear however, on which measure would be sufficient, and as we speak there is still a lot of legal uncertainty around this thorny issue.⁷⁰ The choice made for a specific test and indeed the conclusion that there is infringement on the side of the generic company could potentially have far reaching consequences. In most cases, the generic company will struggle to prevent physicians prescribing cross-label (or even off-label) their generic drug for a patented indication. And liability could

arise by the mere act of the generic drug being prescribed and dispensed for a patented use. If the burden of proof for the generic company is so high that it becomes virtually impossible to avoid infringement, then the business model of generic companies comes under enormous strain. A generic company will always be aware of the fact that it is possible that its products will be prescribed and dispensed for a patented medical indication.⁷¹ This could be because of a preferential use scheme that might be in place in a certain jurisdiction,⁷² or other schemes that favour the prescription of generic drugs with a view to save costs for the national health care system. That might imply that it would become de facto impossible to avoid infringement, which makes the business model for generic companies no longer viable. In the years to come, this issue will eventually need to be sorted out, whether by the courts or by the legislature, who could also intervene to settle the matter.⁷³

It is not difficult to see the immediate parallel with new orphan drug indications and accumulation of regulatory exclusivities. Indeed, reverting back to my first example I gave in this article, if product A has gained a 10 years market exclusivity for the treatment of condition X and subsequently obtains another 10 years of market exclusivity for the treatment of condition Y, there is an infringement risk for a hypothetical generic version of A for X during the exclusivity period of Y, assuming that the drug formulation has not changed. This is an identical scenario to what I explained above in the context of second and further medical use patents. Claiming that the stacking of market exclusivities for the same active substance does not have the potential of a negative effect on generic entry has clearly been demonstrated here to be a fallacy. That is also the reason why we need to remedy this problem sooner rather than later, so as to avoid falling into the same undesirable situation as we have now with medical use patents. In the latter area, we have decided not to think about those issues for the best of 30 years, and we now struggle to find a workable solution. We surely do not want to face a similar situation for orphan drugs.

protection, see, S.J.R. BOSTYN, Patenting DNA Sequences (Polynucleotides) and Scope of Protection in the European Union: An Evaluation, Luxembourg, European Communities, 2004, pp. 56-66 (hereinafter BOSTYN, EC Report 2004).

⁶⁹ See e.g., *Generics (UK) Ltd (t/a Mylan) v. Warner-Lambert Company LLC* [2015] EWHC 2548 (Pat) [10 September 2015]; *Warner-Lambert Company LLC v. Generics (UK) Ltd (t/a Mylan) & Ors* [2016] EWCA Civ 1006 [13 October 2016]; *Carvedilol II* [BGH, Case X ZR 236/01]; *Östrogenblocker* [Case I-2 W 6/17] [5 May 2017]; *Dexmedetomidin* [Case I-2 U 30/17] [1 March 2018], [BeckRS 2018, 2410]; *Fulvestrant, OLG Düsseldorf, Urt. v.*

9.1.2019 – 2 U 27/18, GRUR, 2019, 279.

⁷⁰ This could not have been evidenced better than with the recent UK Supreme Court decision in the *Warner Lambert case relating to pregabalin (Warner-Lambert Company LLC v. Generics (UK) Ltd (t/a Mylan) & Anor* (rev 1) [2018] UKSC 56 [14 November 2018]). Apart from the fact that the patent got invalidated on the basis of “plausibility”, the Lord Justices could not agree on which test should be used to determine infringement of a second medical use patent.

⁷¹ In many cases this will even be materialised in that the generic company will operate under a so-called skinny-label, i.e., the product specification will make reference to

all conditions that could be treated with the generic drug, but it will exclude the patented uses from the label. For more details; see, BOSTYN, IPQ, 2016a, 151-201.

⁷² Under a preferential use scheme, physicians could be stimulated or even be under an obligation to prescribe always a generic version of a drug if there is one, irrespective of whether there is patent protection for the drug for a specific condition or not. For more details, see, BOSTYN, IPQ, 2016a, 151-201.

⁷³ I refer to my 2016 publication to that effect, see, BOSTYN, IPQ, 2016a, 151-201.

Admittedly, it may take a while (as it also took for second medical use patents), but the problems are bound to arise at some point. The reason why it may take a while is that apparently around 70% of the orphan drugs on the market still have primary active patent protection, that is, patent protection for the molecule or biological product as such.⁷⁴ In the presence of those primary patents, there is in most cases no need to revert to market exclusivity, as in most cases that primary patent protection (with the additional of possible SPC granted) will outlast the term of the market exclusivity, and the patent will be used as the instrument for enforcement against third parties. It is, however, a question of time to wait until there is a situation where 1) there is no longer a primary patent and/or 2) patents have been invalidated, and the only exclusivity left is the orphan drug market exclusivity.

We appreciate that, as the total number of orphan drugs on the market is rather small (currently 131 products on the market in Europe), it is difficult to draw very firm conclusions. As said, there are currently around 22 orphan drugs on the European market with multiple indications, which represents a 17% of the total number of authorised orphan drugs. That makes it in practice not easy to evaluate the economic impact of some of the issues we discussed on the pharmaceutical market. That is even more so as many of the orphan drugs have rather modest turnover numbers. The European Commission Staff Working Document draws the conclusion that such a small percentage does not justify immediate statutory change. But the mere fact that it is at this stage not very easy to draw firm economic impact conclusions, should not be seen as an invitation to stop researching those practices and warn for their potential negative economic effects on generic entry. My concern is moreover also informed by the so-called “iceberg” effect, i.e., that this might very well be something that is slowly growing unnoticed, and at some later point in time, we will come to the realisation that we should have acted earlier, very

much alike what has happened with second medical use patents, where we have not realised soon enough the potential generic entry problems. The “iceberg” effect is a very plausible hypothesis indeed, as it is very likely that over time a smaller proportion of orphan drugs will still benefit from primary patent protection, and more orphan drugs will indeed be repurposed drugs. Moreover, personalised medicine has become a reality, and that means in practice more repurposing.⁷⁵ That is, once again, a parallel with the second medical use story in patent law.

4.2 The solutions

Because it is better to act sooner rather than later, I propose in this article a range of solutions to tackle the issues of indication stacking and sub-setting or salami-slicing. As the solutions for both sub-setting and indication stacking are in my view, at least to some extent, different, I will make the proposals also in two different sub-sections.⁷⁶

Sub-setting

As for sub-setting, a number of possible solutions can be conceived:

One is to cluster all subset diseases within one main disease, and let the exclusivity period cover all of them at the same time. In other words, there would be one 10 years period (provided one would consider a 10 years exclusivity period still the best option) covering all those subset diseases of a main disease. For instance, a main type of rare lung cancer would then cover all the subset varieties of that type of lung cancer. The benefit of this solution is clarity and simplicity, as it largely does away with cumulative exclusivities for subsets of a main orphan disease of a certain type. The drawback is that, by taking away almost entirely the potential of sub-setting as a means to gain exclusivity, it might go at the expense of R&D in those areas. Whether that is detrimental can be doubted, as sub-setting is often a means to artificially

⁷⁴ COMMISSION STAFF WORKING DOCUMENT, 2020, Part 3/6, p. 139 (https://ec.europa.eu/health/system/files/2020-08/orphan-regulation_eval_swd_2020-163_part-3_0.pdf). The document lacks a methodology explaining how this percentage was calculated. We know it is quite difficult indeed to link medicinal products as authorised with patents, and the risk for errors is considerable, as multiple patents may cover the same compound.

⁷⁵ See for an explanation of “personalised medicine” and the link with repurposing my, S.J.R. BOSTYN, IPQ 2016a, 153 et seq.

⁷⁶ One could ask questions about the discretionary periods of protection provided in this list of options. All statutory exclusivity

periods are to some extent discretionary. For instance, the US orphan drug system provides a statutory market protection period of 7 years, whilst the European system provides a period of 10 years. The justification for this difference is, at least according to some, only explained as a desire to provide a more competitive exclusivity than the US system (see, European Union Review of Pharmaceutical Incentives: Suggestions for Change, Medicines Law and Policy, June 2019, p. 47: <https://medicineslawandpolicy.org/wp-content/uploads/2019/06/MLP-European-Union-Review-of-Pharma-Incentives-Suggestions-for-Change.pdf>). As the statutory exclusivity periods do not seem to have a firm basis in

science, the solutions provided in this article suggest exclusivity periods which seem reasonable and fair, even though admittedly not founded in science.

⁷⁷ There is of course always the patent system to protect those new indications, provided all patentability requirements can be fulfilled.

“create” new rare diseases based on even deeper gene profiling.

The above solution is very much akin to introducing the concept of GMA for “regular” drugs to sub-setting. That would imply that new indications would not be entitled to their own 10 years period, but could at best, for one new indication showing significant clinical benefit, a 1 year market exclusivity extension.

A second option could be to allow the “salami” to be of a certain size and to be “sliced” up a limited number of times. One could for instance think of a scenario where the applicant could only gain exclusivity protection for 2 or 3 subsets. Any further sub-setting would be without the benefit of an additional exclusivity.

A third option could be to allow sub-setting with exclusivity periods. But each of the subsets would only gain a shorter period of exclusivity, which could for instance be 3 years. That would still provide an incentive, but would have a much less negative effect in terms of delay for generic entry. That option could be combined with option 2, and should perhaps preferably be combined with option 2.

A fourth option in the context of sub-setting is to allow it under any of the above options, but to legislate specifically that the holder of any subsequent exclusivity period will not be entitled to sue for infringement against a third party who sells products that are not brought to market for the still protected indications (skinny labelling), but which could be prescribed for the protected use, save as for one exception. That exception would be that the third party deliberately markets the product for the protected indication.

Indication stacking

In relation to indication stacking, we also present a number of options. Indication stacking can take place in the context of sub-setting, but that does not necessarily have to be the case, as one could conceive repurposing the active substance to a rather different disease.

To the extent that the indication stacking takes place in the context of sub-setting, the options discussed below will indicate the consequences.

Option 1 could be to copy the system for “regular” drugs, and introduce the concept of GMA also for orphan drugs. That would imply that new indications would not be entitled to their own 10 years period, but could at best, for one new indication showing significant clinical benefit, a 1 year market exclusivity extension.

The benefit of this solution is clarity across the spectrum of pharmaceutical products. The drawback is that it might take away incentives for companies to invest in R&D in repurposing drugs for new orphan diseases.⁷⁷ As I have already explained, I do not think that there would be negative consequences in the case of indication stacking in the context of sub-setting, for the reasons already explained above in the context of sub-setting.

A second option could be to allow indication stacking for the same or similar pharmaceutical product, but each of those new indications will only be allowed a shortened period of exclusivity. That could for instance be 3 years.



The first orphan indication of an already existing or new active substance would be entitled to 10 years of market exclusivity, but each subsequent one only 3 years.

If indication stacking takes place in the context of sub-setting, this could be combined with a limitation to the number of subsets that create entitlement to an additional exclusivity period.

A third option could be to reduce the base period of 10 years for all orphan drugs. That could for instance be 5 or 7 years, and an extension could be obtained up to a maximum of 10 years in total upon providing evidence that no sufficient return on investment has been obtained within the period of 5 or 7 years. All further indications would then be entitled to the abovementioned 3 years. Alternatively, further indications would not gain any additional exclusivity period, in line with the GMA concept. Once again, if indication stacking takes place in the context of sub-setting, this could be combined with a limitation to the number of subsets that create entitlement to an additional exclusivity period.

A fourth option would be to take inspiration of the “salami slicing” scenario. Indication stacking with accompanying exclusivity periods would be allowed, but only for a limited number of indications. Once the “quota” has been exceeded, no further exclusivity could be obtained. The drawback of this solution is that it could disincentivise R&D and marketing of new orphan indications. If the indication stacking is in the context of sub-setting, granting no further exclusivity is without harm, as explained earlier. But if the new indication is not in the context of sub-setting, then there is the risk that companies will not have sufficient incentives to carry out research into new orphan drug indications.

A fifth option in the context of indication stacking is to allow it under any of the above options, but to legislate specifically that the holder of any subsequent exclusivity period will not be entitled to sue for infringement against a third party who sells products that are not brought to market for the still protected indications (skinny labelling), but which could be prescribed for the protected use, save as for one exception. That exception would be that the third party brings the product to market and/or deliberately markets the product for the protected indication, in which case there would be liability for infringement and right to damages.

A sixth proposal is to introduce the same concept of what is the same marketing authorisation holder as we know for “regular” drugs. It is under the orphan drug system possible to give consent to a third party to bring on the market a similar medicinal orphan drug product for the same medical indications, and that consent will trigger in itself a new 10 years period of exclusivity.⁷⁸ For example, Novartis Germany could in that connection give consent to Novartis Switzerland, and a new 10 years exclusivity period will be triggered. Leaving aside the absence of cumulative exclusivity periods under the “regular” drug system, the definition of marketing authorisation holder is also defined broadly:

“An ‘applicant’ and ‘marketing authorisation holder’ can be a physical or legal entity. However, for the purposes of the application of the pharmaceuticals rules, having a distinct legal personality does not necessarily entail that each entity can be considered as a distinct applicant or marketing authorisation holder to the other one. In particular, it is noted:

- Applicants and marketing authorisation holders belonging to the same company group or that are controlled by the same physical or legal entity are to be considered as one entity.
- Applicants and marketing authorisation holders that do not belong to the same company group and are not controlled by the same physical or legal entity are to be considered as one applicant/marketing authorisation holder if they have concluded tacit or explicit agreements concerning the marketing of the same medicinal product for the purposes of the application of the pharmaceuticals rules regarding that medicinal product. This includes cases of joint marketing but also cases where one party licenses to the other party the right to market the same medicinal product in exchange for fees or other considerations.”⁷⁹

By using a similar broad definition in the area of orphan drugs, one would fundamentally take away the incentive that different subsidiaries give each other consent (triggering a new 10 years exclusivity period), that holdings would do the same with subsidiaries, or that there would otherwise be an agreement between two companies. I do not see fundamental drawbacks to the research incentive system by doing so.

A seventh option is to replace exclusivities for new indications with a transferable voucher system. Such a voucher would allow the holder of the voucher (which provides a temporary market exclusivity) to sell it to an interested party and gain capital in return, which can be invested in further R&D. Transferable vouchers present problems though. It is very likely that they will be used so as to provide additional market exclusivity to block buster drugs (as such use will most likely generate the highest income for the transfer of the voucher), which in turn implies a further delay of generic entry for such block buster drugs. In that sense, I am myself quite sceptical towards the added value of transferable vouchers.

5 CONCLUSION

In this article, I have demonstrated that the orphan drug system is in need of amendment. This is in particular the case for the practices of sub-setting and indication stacking. The main argument to delay action in this regard that the percentage of indication stacking cases is relatively small (17%) is not convincing in my view, as we have seen also with second medical use patents that it takes often a very long period during which the “iceberg” grows, and once the size of the problem becomes apparent, the damage caused is often already considerable.

In order to avoid the negative effect of the abovementioned “iceberg” phenomenon, I have made a wide range of proposals for change. In my view, action must be taken sooner rather than later. Regulating for the future is better than remedying the past.

⁷⁸ See Art. 8(3) Regulation 141/2000/EC: “By way of derogation from paragraph 1, and without prejudice to intellectual property law or any other provision of Community law, a marketing authorisation may be granted, for the same therapeutic indication, to a similar medicinal product if: (a) the holder of the marketing authorisation for the original orphan medicinal product has given his consent to the second applicant, [...]”

⁷⁹ NOTICE TO APPLICANTS, VOLUME 2A

Procedures for marketing authorisation
CHAPTER 1 MARKETING AUTHORISATION,
July 2019, section. 2.8, p. 14.

With regard to sub-setting, proposals range from taking away all further exclusivities after the “base” period of 10 years for any further subset to grant only short periods of exclusivity for a limited number of subsets (smaller salami with defined size slices).

In the context of indication stacking (which can go hand in hand with sub-setting, but does not need to), proposals range from introducing the GMA concept also for orphan drugs, de facto eliminating stacking of exclusivities, to also limiting the number of indications that can attain an additional exclusivity period of a limited duration.

We have finally also brought up the idea of reducing the base period of 10 years to for instance 5 or 7 years, with the possibility to gain an extension totalling 10 years provided it can be evidenced that no reasonable return on investment has been achieved within the base period. New indications could then 1) gain no additional exclusivity periods (in line with the GMA concept), or 2) attain a limited exclusivity period of for instance 3 years.

The purpose of the present article was to provide a document for further informed discussion in the process of reviewing the orphan drug exclusivity system in Europe. I hope that my proposals will indeed lead to such a fruitful discussion, and that action is taken by the European Commission to make the orphan drug system more performant, but at the same also take into account the interests of patients to get access to reasonably priced orphan drugs with the highest possible degree of competition between providers. To that effect, generic entry delay strategies should be a policy priority.



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