Non-Patent Exclusivity Strategies for pharmaceuticals

By Peter Holm and Jens Viktor Nørgaard, HØIBERG A/S June 2015

Development of pharmaceuticals is both expensive and time consuming, often with development processes of up to 10-15 years before market authorization. In order to obtain a reasonable return of investment it is thus important to secure appropriate exclusivity for the pharmaceutical product or process, once it has obtained its marked approval. Strategies for maximizing patent protection and life cycle management has been outlined in our earlier newsletter entitled "Clinical trials and patenting". While patenting is the main route to exclusivity, the duration is only 1+20 years counted from the priority date. This period sometimes does not leave sufficient time for a reasonable return of the extensive investments made. When planning the exclusivity strategy, it is therefore important to consider additional exclusivity strategies like patent term extensions, and various types of data exclusivity such as orphan drug exclusivity and paediatric exclusivity, in addition to conventional IP rights like patents, trademarks and design.

Although no uniform system or nomenclature exists to date for the various types of exclusivity available in different countries, the following table summarises the main exclusivity types in the four most patent intense jurisdictions.

	Duration			
Type of Exclusivity	**Europe**	**USA**	**Japan**	**China**
Delay by health authority approval	N/A	30 months	N/A	N/A
SPC/PTE	≤5 years	≤5 years	≤5 years	N/A
Data Exclusivity / NCE	8+2+1 year	5 years	8 years	6 years
Orphan Drug	10 years	7 years	10 years	N/A
Paediatric	6 months	6 months	≤2 years	N/A
New use / formulation (Clinical Investigation Exclusivity)	N/A	3 years	4/6 years	N/A
Biologics license application (BLA)	N/A	12 years	N/A	N/A

Delay by health authority approval

In the USA the "Orange Book" identifies drug products approved on the basis of safety and effectiveness by the Food and Drug Administration (FDA). The Orange Book also lists patents that are purported to protect each drug approved by the FDA. When the producer of a generic drug seeks market approval for their product, they must file an Abbreviated New Drug Application (ANDA) which is an application for a generic drug approval for an existing licensed medication or approved drug. Under the Hatch-Waxman Act the FDA may refuse to issue an ANDA to a generic drug producer for up to 30 months. This procedure has no equivalent in Europe, Japan or China.

Patent Term Extension

The European Supplementary Protection Certificate (SPC) in Europe, and its analogue in the USA and Japan denoted Patent Term Extension (PTE) are systems designed to extend the term of a patent for a certain pharmaceutical. Although individual differences exists, the system aims to compensate the drug developer having a patent covering the product undergoing clinical trials, for the delay before regulatory approval of the drug.

The extension requires a valid and unexpired patent and only one patent may be extended per approved drug. China currently does not provide a system for patent term extension, despite the fast growth in pharmaceutical research in China. The Chinese government has adopted a cautious policy in order not to burden the overall pharmaceutical industry and limiting public access to affordable medicine. Due to the limitations in PTE and other exclusivity options as outlined herein below, it is particularly important to carefully consider the timing for filing a patent application directed to a pharmaceutical drug. Filing too early in relation to clinical trials may lead to that the patent expires before the drug receives its MA; and filing too late may of course jeopardize novelty of the patent. An alternative both for China and the rest of the world may be to apply a tiered patenting strategy where a first generation patent is obtained for the basic active compound, a second and further generation applications are filed to cover other aspects of the drug, such as salts, esters, hydrates, polymorphs, new formulations, new administration routes, and new indications as the data becomes available. In this respect we refer to our earlier newsletter relating to clinical trials and patenting.

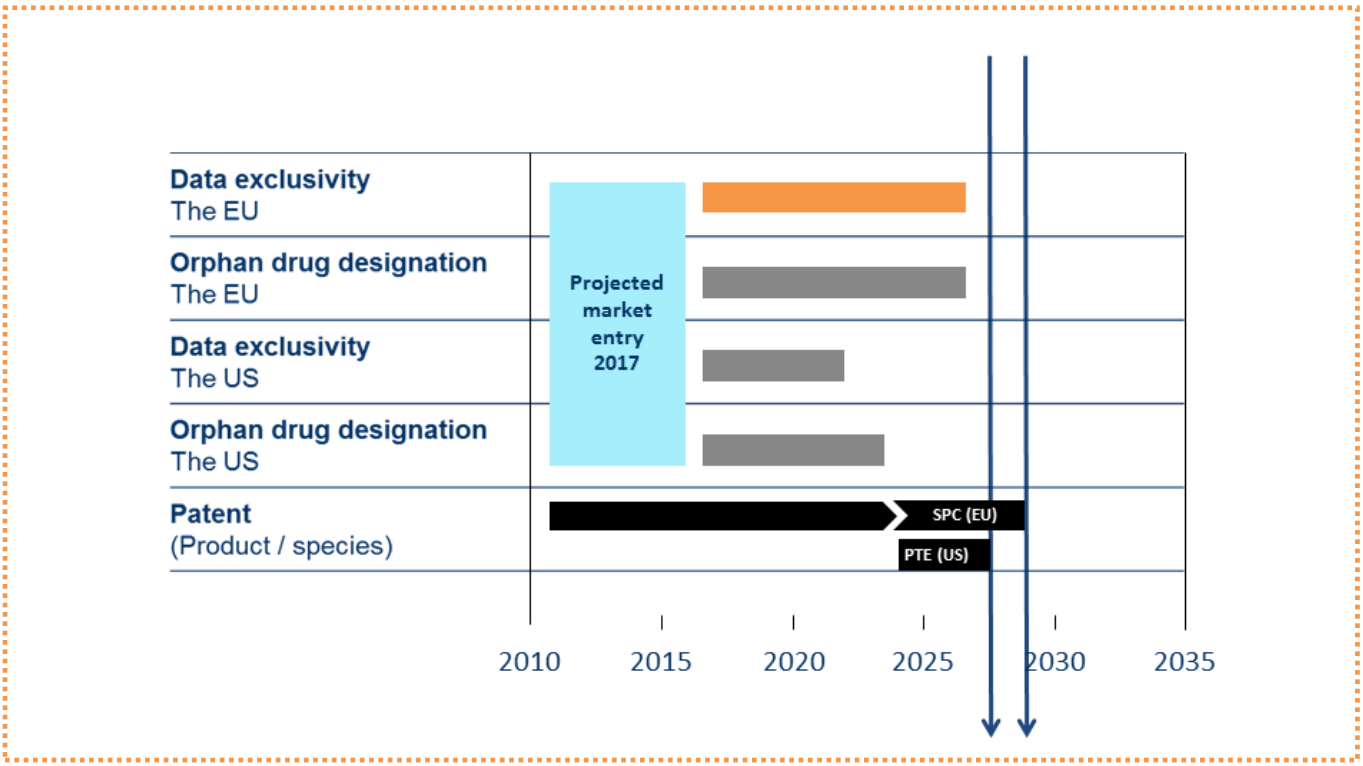

Figure 1: Example of the interplay between patent and non-patent based exclusivities.

Data exclusivity

When a company has conducted the demanding clinical trials of a pharmaceutical drug, resulting in a marketing authorisation (MA), there is no benefit for society to duplicate this process for other parties seeking market authorisation for the same or a similar drug. On the contrary duplication would be a loss for society. Additionally, it is ethically dubious to expose yet another group of patients to the same drugs, with the mere purpose of putting a generic drug on the market following expiry of the patent protection for the original drug. For these reasons clinical results of an earlier trial can be referenced in a later application for MA essentially of the same or essentially the same drug. However, in order to promote development of new and better drugs, hopefully to the benefit of society, the developer of the original drug is awarded with data protection/clinical investigation exclusivity by the regulatory authorities. This means that an application for market authorisation by a third party of a generic drug, with reference to the clinical data of the original drug, is not accepted by the regulatory authorities for a limited period.

Europe

The data exclusivity directive of the European Union (EU) allows for up to 11 years of exclusivity for a party, to market their product without competition. The 11 year period is divided into 8 years of data exclusivity, 2 years of marketing exclusivity, and a further optional year of extension. During the 8 year period the regulatory authorities may not approve marketing authorisations for generic versions of the drug protected by the data exclusivity.

In practise the protection is implemented by having it treated as a trade secret, where generics manufacturers cannot reference the protected data prior to the expiry of the 8 year exclusivity period. A 3rd party wanting to apply for marketing authorization (MA) during the mentioned exclusivity period must instead perform its toxicology and safety studies, and its own clinical trials, without relying on the data relating to the protected drug.

When the 8-year data exclusivity period ends, manufacturers of generic drugs can elect to rely on the data from the original reference drug to demonstrate the generic drugs's bioequivalence, necessary to gain MA.

In the 2 year period of marketing exclusivity following the preceding 8 year data exclusivity period, the regulatory authorities will not approve a marketing authorisation for the generic product.

Finally, the proprietor of the marketing authorisation for the original drug can obtain a 1-year extension of the above mentioned 2-year marketing exclusivity.

The Data Exclusivity Directive includes a proviso that patent laws in EU member states should not prevent 3rd parties from conducting studies and trials necessary to obtain marketing authorisation for generic products. In this respect we also refer to our previous newsletter concerning research use exemptions.

United States

In the USA, data exclusivity can be divided into (i) New Chemical Entity (NCE), (ii) Clinical Investigation Exclusivity (CIE), and (iii) BLA. Sometimes orphan drug and paediatric exclusivity is also included under the generic term data exclusivity. For clarity reasons we will however separate these topic in the present article.

Under the NCE exclusivity, the first applicant to receive approval for a product containing an active moiety that is a so called new chemical entity (a small molecule) is awarded with a 5-year period of data exclusivity. During this 5-year period, no other party can submit a New Drug Application (NDA) or an abbreviated new drug application (ANDA) seeking regulatory approval of a drug product containing the same active moiety.

Under the CIE, sometimes referred to as new use or new formulation exclusivity, 3 years marketing exclusivity is awarded for new dosage forms, new indications and a product's change from prescription to over-the-counter. During the 3-year period FDA may not approve an ANDA.

Under the BLA exclusivity, the first applicant to receive approval for a product containing an active moiety that is a so called biologics product is awarded with a 12-year period of data exclusivity.

Japan

The data exclusivity period is referred to as the "Re-examination period" in Japan. The underlying legislation applies to both "regular drugs" and

"orphan drugs" and awards 8 and 10 years respectively, of exclusivity.

China
In China data protection is only available for drugs containing new chemical ingredients. The exclusivity period is 6 years from the date of the original applicant's marketing authorisation by the Chinese regulatory authority. During this period, a drug application using the original applicant's undisclosed data without express consent will not be approved in China. Publicly disclosed data from the original applicant, can however be used in another drug application within the data protection period which renders the data protection in China to be fairly weak as compared to EU or the US. It is however expected that the situation will change in the near future, as amendments of the Pharmaceutical Administration Law has been included in the current five-year legislature plan of the Chinese National Standing Committee. The Chinese FDA is also in the process of collecting comments regarding issues on the enforcement of the current Pharmaceutical Administration Law. It is thus advisable to stay informed to be up to date with the fast transforming Chinese society.

Orphan Drug exclusivity

Diseases and disorders afflicting very few individuals are jointly referred to as orphan diseases. Consequently drugs aimed at treating these diseases are referred to as orphan drugs. The incite for drug developers to invest in the costly clinical development of orphan drugs for treatment of orphan diseases is thus limited. To promote development of orphan drugs, the regulatory authorities in many countries have implemented legislation providing specific protection for orphan drugs. Although differences exist between various countries, orphan drug exclusivity is typically obtained by non-acceptance by the regulatory authorities, of applications for marketing authorisation by third parties seeking to market their drugs for treatment of the same orphan disease. The non-acceptance period, i.e. the exclusivity period for a certain orphan drug/orphan disease combination is a number of years from the date of market authorisation for the original orphan drug/orphan disease combination.

The orphan drug exclusivity are dispensed with if the proprietor of the exclusive market authorisation is unable to provide the market with sufficient amounts of the orphan drug, as well as when a later application for MA-authorisation concerns a drug which is safer, more efficient or in other way clinically superior to the earlier orphan drug.

Europe
In the EU, an orphan indication is:
(a) intended to diagnose, prevent, or treat a life-threatening or very serious condition i) afflicting no more than five in 10,000 people in the EU; or ii) that, without incentives, would probably not be marketed given its low likelihood that the marketing would generate sufficient return to justify the investment; or (b) there must not be any satisfactory method of diagnosis, prevention, or treatment in the European Community, or if a method does exist, the medicinal product should be of significant benefit to those affected by the condition.

The orphan drug regulation establishes a centralised procedure for the EU under which it is possible to apply for orphan drug designation. The applicant should submit the application for orphan designation prior to the application for MA. The European Medicines Agency (EMA) is responsible for reviewing and granting orphan drug applications.

If marketing authorisation is granted under EU's centralised procedure or by all member states, the community and the member states will not, for a period of 10 years, accept or grant another application for MA, or accept an application to extend an existing marketing authorisation, for the same therapeutic indication with respect to a similar pharmaceutical product.

To date, no centralised validation procedure is available for European Patents granted by the EPO. Since the national validation procedure is costly, most proprietors of European Patents elect only to validate in a number of key EPC contracting states thus leaving other countries open without patent protection. The benefit of orphan drug designation in the EU is therefore highly beneficial for entities working with orphan indications.

USA
In the US, orphan indications are defined as disorders affecting less than 200,000 individuals in the US. The orphan drug status allows 7 years of marketing exclusivity, during which period the FDA is prevented from approving the same active drug for the same indication.

FDA may however accept and approve applications for drugs having the same active moiety, for a different indication. In addition, FDA may accept and approve a subsequent orphan drug application for the "same drug" and the "same orphan indication," if the applicant demonstrates that the product is "clinically superior", safer, more effective or significantly more convenient than the first drug.

This provides an incentive for drug companies to continue to develop innovative and effective products for the orphan drug market.

Japan
As mentioned above, in Japan orphan drugs are included under the legislation for data exclusivity, by virtue of which "orphan drugs" are awarded 10 years of market exclusivity.

China
In China, an orphan indication is a disease which has a prevalence of <1/500,000; or has a neonatal morbidity of fewer than 1/10,000. China is actively preparing to regulate and encourage the development of orphan drugs, but still lags far behind the EU, USA and Japan, with orphan drug legislation. The current regulations only set forth general criteria to accelerate the registration and approval of orphan drugs, but detailed rules have not been implemented and further incentives have not been proposed until now. The tiered patenting strategies outlined under data exclusivity above is still a relevant consideration for optimising drug exclusivity in China.

Paediatric exclusivity
Children often respond different to pharmaceutical drugs as compared to adults. Historically, little drug testing was conducted in paediatric populations. The lack of paediatric data has raised concerns regarding use of drugs approved for adults, for treatment of the same diseases in children. To promote paediatric drug development and clinical testing, many countries have implemented an additional period of exclusivity for drugs tested in paediatric populations.

Europe
The paediatric exclusivity in the EU is basically a 6 month extension of an existing SPC awarded to applicants who, in their MA application include clinical data of their product's use in children resulting from a paediatric investigation plan (PIP).

The 6 month extension will apply, not only to the product's paediatric indication, but to all indications of the product having the same active ingredient. The SPC term extension will not be available if the applicant instead obtains a 1-year extension of the products' marketing protection "on the grounds that the new paediatric indication brings a significant clinical benefit in comparison with existing therapies."

The paediatric legislation also provides for a new type of marketing authorisation, the Paediatric Use Marketing Authorisation (PUMA), for medicinal products not protected by SPC or the preceding SPC qualifying patents. PUMAs may provide eight years of data exclusivity and 10 years marketing exclusivity for those products developed exclusively for use in a paediatric population.

USA
Unlike in Europe, paediatric exclusivity in the US adds a 6-month period of marketing exclusivity to any existing non-patent exclusivity. Paediatric exclusivity, once attained for a drug, applies not only to the specific drug product studied in the paediatric population, but to all of the applicant's dosages, formulations and indications for drugs with existing marketing exclusivity or patent life that contain the same active ingredient. A paediatric study does not have to be successful for the applicant to obtain paediatric exclusivity.

Japan
Paediatric exclusivity in Japan is a part of the re-examination system which includes data exclusivity and orphan drug exclusivity. The paediatric exclusivity period is like in Europe or the US awarded for clinical trials conducted on paediatric populations, and is added to another non-patent based exclusivity such as orphan drug exclusivity. Depending on the conditions, paediatric extension in Japan can be up to 2 years.

China
China does not provide marketing exclusivity in exchange for conducting paediatric clinical trials or require submission of such studies with marketing applications. Recently however, six government ministries in China met and issued a joint opinion that set forth policy measures aimed at improving development, access to, and use of drugs formulated for paediatric use. It is therefore likely that incites for better drugs for the paediatric population will be implemented in the future. Paediatric exclusivity is likely to be one such incite.

Biosimilars

For biological products, it is difficult to prove the equivalence of active ingredients with those of existing drugs unlike with chemically synthesized drugs, but with the advances made in technology, biosimilars (or follow-on biologics) have been developed in recent years as products with equivalence to and the same quality as existing biological product. In the USA, new legislation was enacted in 2010 which encourages innovation and promotes competition for biological products by awarding these up to 12 years of exclusive use of a reference biological products before biosimilars can be approved for marketing. No similar legislation discriminating biologics from other pharmaceuticals is available in Europe, Japan or China to date.

Conclusions/Recommendations

- Taking advantage of the multiple forms of market exclusivity available the various jurisdictions.
- Develop a long term exclusivity strategy that includes the various testing and development activities required.
- Plan your exclusivity strategy already when drafting the clinical study protocols.
- Considering what to do if your product patent expires before MA of the product is introduced to the market.
- Consider if your product is available for an orphan population.
- Consider conducting paediatric studies.
- Are there other indications for the product in the pipeline?

If you have any questions you are very welcome to contact your patent attorney at HØIBERG A/S.

Peter Holm

Partner, European Patent Attorney

Contact information:
T: +45 3332 0337
phm@hoiberg.com
Learn more about Peter Holm here.

Jens Viktor Nørgaard

Partner, European Patent Attorney

Contact information:
T: +45 3332 0337
jvn@hoiberg.com
Learn more about Jens Viktor Nørgaard here.