

Regulatory Exclusivities or Non-patent exclusivities

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Abstract

Pharmaceutical development is an expensive, time consuming and uncertain process that takes years to complete. Often, patent protection expires before a new drug is approved for marketing. As a result, most pharmaceutical companies in the United States and European Union (EU) depend on the exclusivity rights granted under the U.S. Federal Food, Drug and Cosmetic Act (FDCA), and the corresponding EU authorities to recoup their considerable investment in the drug development and approval process. Therefore, pharmaceutical companies must understand and employ the different forms of nonpatent exclusivity in both the U.S. and EU in order to succeed in the global marketplace.

Keywords: Pharmaceuticals; Drug development; Patent; Regulatory exclusivities

Introduction

The Process of development of a pharmaceutical is time taking, costly and uncertain. The long-time duration of the process may result in expiry of the patent term before the marketing of the product. To overcome this difficulty the United States and European Union (EU) have advised the concept of exclusivities which help in recovering the investment that was made in the process. The product can be marketed during the period of exclusivity without any competition from its generic form.

Regulatory Exclusivities are also called *non-patent exclusivities* as they help in extension of market protection of product beyond the patent term [1-3].

Exclusivities in the US

The pharmaceutical companies have to apply for exclusivities but the New Chemical Entity Exclusivity and the Clinical Investigation Exclusivity are granted by the Drug Competition and Patent Term Restoration Act or the Hatch Waxman Act and do not require any type of application. They come into effect directly when a new chemical entity is introduced in the market and when clinical trials are being conducted for supporting changes in already marketed products [4,5].

New chemical entity (NCE) exclusivity

An active moiety is a molecule or ion that is responsible for bringing about the physiological or pharmacological action of the drug substance. If the active moiety in the proposed drug product is new and does not match with any of the previously approved moieties, then such a product gains eligibility for the NCE Exclusivity for a period of up to 5 years.

During this period, the FDA is not entitled either to approve or accept an ANDA or a 505 (b) (2) application based on the NDA of the NCE containing product, whether the ANDA or 505 (b) (2) application intends to introduce the drug for the same indication or for different indication. The drug product may thus enjoy exclusive marketing for a period of up to 7 years as the FDA cannot even accept an ANDA for review during NCE Exclusivity term. The ANDA is accepted for review after the 5 year term and it takes almost 2 years on an average for approval of the ANDA, thus making the period of exclusive marketing as 7 years or even more.

However, NCE Exclusivity gained by NDA does not prevent the

FDA from accepting or approving another NDA whose proposed product contains the same active moiety but the NDA is supported by clinical trials conducted by the applicant himself [6].

Clinical investigation (CI) exclusivity

When sponsors of already marketed products conduct clinical trials to support changes in their products related to its dosage form, its indications, its prescription status (from OTC to prescription), etc., then they become eligible for grant of CI Exclusivity. The term of this exclusivity ranges up to 3 years and is applicable when the clinical trials that are conducted are new (not carried out previously in support of the original NDA), essential for approval, sponsored by the applicant and do not constitute just a bioavailability study [7].

These clinical studies, may be carried out to support changes related to:

1. The product being formulated with new dosage strength (NS Exclusivity).

Example: A 10 mg tablet being developed for a product that was earlier approved as a 5 mg tablet.

2. The product showing efficacy for a new indication.

3. The product being formulated as a new dosage form (NDF Exclusivity).

Example: A drug substance being formulated into capsule form from an earlier approved tablet form.

4. The product being developed to be administered through a new route.

Example: An approved intravenous formulation being developed to be administered through sublingual route.

5. The product being developed using different excipients or

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different concentration of excipients from that in the earlier formula.

During this period of exclusivity, the FDA is not entitled to approve a competitor's ANDA or other application based on the same change that the clinical trials support for the original NDA. However, the FDA can accept such an ANDA for review but holds its approval till the expiry of the CI Exclusivity. The CI Exclusivity does not prevent the FDA from accepting or approving either an ANDA that is related to the original indication of the product, or an NDA that is related to the new changes in the product but supported by its own clinical trials.

Orphan drug exclusivity (OED)

Orphan drugs are those that are used in the treatment of diseases and conditions that affect 2,00,000 or fewer Americans, or for which the market in the US is small leading to inability of the sponsor to recover the investment that was made in the development process of such a product [8].

The small market associated with these drugs may make the companies hesitant to carry out research in this area or even if the products are developed, they will be marketed at exorbitant prices. To overcome these drawbacks, the Orphan Drug Act in 1983 which helped in encouraging innovation in this field. According to the Act, manufacturers who develop such drugs are entitled to a period of 7 years of marketing exclusivity (ODE) along with research grants and tax credits [9].

During this period of exclusivity, the FDA is not entitled to approve but accept for review any application for generic or second innovator products that consist of the same active moiety and proposed with the same indications. However, FDA can accept and approve an application for a product containing the same active moiety but proposed for a different indication.

Even an application for a product containing the same active ingredient and proposed for the same orphan indication can be accepted and approved by the FDA if it demonstrates a safer or more effective drug profile or a greater convenience of use than the original product.

Pediatric (PED) exclusivity

The Best Pharmaceuticals for Children Act was passed in 2002 to encourage pediatric drug development and testing as the metabolism of drug products and the response to them may be different children. Thus, products for which pediatric safety is assessed by way of clinical studies on pediatric population are granted PED Exclusivity for a term of six months in addition to the patent term which they already possess (NCE or Orphan Drug Exclusivity). This exclusivity does not exist independently but is an extension of the already existing exclusivities or patent on the product [10,11].

The applicant may conduct pediatric studies for a product upon receipt of a written request from the FDA asking for the evaluation of efficacy and safety of the drug in pediatric populations. Upon completion of the study, the sponsor is granted pediatric exclusivity irrespective of the study being successful or not. The grant of such an exclusivity extends to not only the present product but to other dosages, formulations and indications for drugs with existing marketing exclusivity or patent term that consist of the same active moiety.

Patent challenge (PC) exclusivity

PC exclusivity also called the 180-day generic product exclusivity

is granted to encourage companies developing generic product, to challenge existing patents on grounds of it being an improperly granted patent.

A first to file ANDA with Paragraph IV certification has the right to obtain this exclusivity. The sponsor of these ANDA gains huge profits during this period as it sells its product at a price that does not show much difference from the innovator's price, without any competition from other generic products.

The procedure for filing PC Exclusivity includes submission of a complete ANDA for a drug product listed in the Orange Book and such an ANDA should challenge a patent listed in the Orange Book by way of Paragraph IV certification. When the exclusivity is granted, the FDA is not allowed to approve another ANDA for the same drug product for the same indication. The term same drug product is used for a drug product that has the same dosage form and strength. An ANDA of the same product with difference strength can be approved by the FDA during this exclusivity period [12-14].

The 180-day exclusivity may lapse in following cases.

- a. If the sponsor fails to market the product within 75 days of approval of the ANDA or 30 months from the filing of ANDA whichever is earlier, or within 75 days from a decision about the patent being invalid or not being infringed.
- b. If a sponsor fails to commercially market the product within 75 days from the date on which a second ANDA applicant obtains a final judgement on invalidation of the challenged patent.
- c. If an ANDA applicant withdraws its application, or changes or withdraws its Paragraph IV certification.
- d. If the ANDA applicant signs an agreement with the NDA holder or another generic company, provided such an agreement is termed as anti-competitive by a court.
- e. If the patent for the listed drug product expired before the marketing of the generic product. However, this forfeiture is valid only when the patent expires or is delisted by the inventor before filing of Paragraph IV notice. In case the inventor delists the patent or does not pay the patent fee to make it expire after the filing of Paragraph IV notice by the generic, the generic is still given the PC exclusivity.

Exclusivities in the European Union

Supplementary protection certificate

Supplementary Protection Certificate (SPC) are unique, national rights that come into effect upon the expiry of patent and are granted with an objective of providing marketing exclusivity even after the expiry of patent. They are granted to compensate for the loss incurred due to huge time lapse between the grant of patent and the grant of marketing authorization of the product. The practice of granting SPC's was started in 1993. They are only when the product is protected under a patent, holds a marketing authorization as a product intended for medicinal use and has not been previously given a SPC [9].

The period of marketing exclusivity granted through SPC can be calculated by subtracting 5 years from the time elapsed between the grant of patent and the grant of marketing authorization. However, a maximum period of 5 years of marketing exclusivity is granted even if the calculated period exceeds this limit. A six month extension on this period is granted to the SPC term if the sponsor carries out pediatric studies with the product.

EU Data exclusivity “8+2+1”

A pharmaceutical company is given up to 11 years of marketing exclusivity by following an 8+2+1 pattern wherein 8 years comprise data exclusivity period, 2 years comprise marketing exclusivity period and one year is an extension period.

Generic applications cannot be submitted for obtaining marketing authorization during the period of data exclusivity. The innovators data cannot be used even for reference during this period and is considered as trade secret. If a company intends to submit an application on the same product during the period of data exclusivity of the innovator, then it should conduct its own clinical trials, safety and toxicological studies without depending on the innovators data. Though the data exclusivity prohibits submission of generic applications, it does not stop the sponsors of these generics from conducting studies and trials that are required for obtaining their marketing authorization [15,16].

At the expiry of the data exclusivity period, the two year marketing exclusivity term begins. During this period generic developers may take reference from the innovators data, however they are not granted marketing authorization. If the company gains approval for one or more new indications of the innovator product making it more beneficial over existing therapies during the data exclusivity period, then the product is given a further one year of marketing exclusivity. Thus, competition from generic drugs is reduced for one more year as they cannot be granted marketing authorization during this period.

Orphan drug designation

The EU orphan Drug Designation was passed on December 16, 1999 and was enforced on April 27, 2000. Incentives are allotted through this regulation for companies that carry out research development if orphan drugs in order to encourage innovation in this field.

- a. A drug which is intended to be used for diagnosis, prevention or treatment of a life-threatening or very serious condition that affects not more than 5 people in 10,000 in EU.
- b. A drug which is intended to be used for the diagnosis, prevention or treatment of a life-threatening or very serious and chronic condition whose marketing would not be able to recover the investment made in its research and development. If no incentives are given to those drugs, it results in failure of their marketing.

Along with the above criteria, no other therapies should be available for the diagnosis, prevention or treatment of the condition or the present drug product should be more beneficial than the existing therapies to be granted the orphan drug designation.

The application for grant of orphan drug designation should be submitted using centralized procedure and such a submission should be made before any application for marketing of the drug is made (i.e., application for obtaining marketing authorization is made). This application is reviewed by the EMEA's Committee for orphan Medicinal Product (COMP), which is required to give its opinion within 90 days of the submission. If the COMP gives a positive opinion, the application is forwarded to the European Commission which takes a decision within 30 days [17].

The grant of orphan drug designation offers many benefits to the manufacturer. If the grant is through a centralized procedure or is accepted by all Member States, then a marketing exclusivity of 10 years

is given to the drug and during this period nobody from the community or the Member States is allowed to accept a second application for a marketing authorization, to grant a marketing authorization or to accept an application for extension of an existing marketing authorization pertaining to the similar medicinal product. The term similar medicinal product refers to a product which contains the same active moiety or the same principal molecular structural features and shows its action through the same therapeutic indication.

The other benefits of the designation are, the sponsor being given access to advice from EMEA on the requirements for obtaining marketing approval, the marketing approval being given on the wider scale through centralized procedure, and exemption or reduction of the marketing authorization fee for the sponsor.

The period of marketing exclusivity may get extended to 12 years in case of pediatric products. It may also be reduced to six years if the profit earned by the marketing of drug at the end of the fifth year of exclusivity is such that it can no longer be categorized as an orphan drug. Other instances wherein the product loses its exclusivity are when the sponsor agrees to a second orphan drug application, or when the sponsor is unable to meet the demand for supply of the drug.

An application can also obtain marketing authorization for a drug similar to the orphan drug similar to the orphan drug if he can prove that his drug is safer, has greater efficacy or is better in some aspects compared to the existing orphan drug [18].

Pediatric exclusivity

The Pediatric Regulation establish the grant of a six-month extension on existing SPCs (pediatric exclusivity) and a type of marketing authorization called the Pediatric Use Marketing Authorization (PUMA).

The regulations requires the sponsor to carry out pediatric studies using the drug, following the pediatric investigation plan (PIP) and the data from these studies is to be submitted in the application for obtaining marketing authorization. Even the applications for varying or extending of a marketing authorization of an already marketed drug (eligible for an SPC or protected by SPC) as a result of development of new pharmaceutical form, discovery of a new indication or a new route of administration, should also contain data from pediatric studies.

All the applicants are required to carry out these studies as per PIP except.

- a. Those which have been exempted from such studies or,
- b. For which the studies have been allowed to be conducted at a later date.

The sponsor whose applications contain the data from pediatric studies can apply for a six-month extension to the product's SPC, which if granted applies to not just the specific indication but to all indications of the products containing the same active moiety. However, this extension does not apply for products which have already been granted a one-year extension on the exclusivity term on grounds of the product showing a new pediatric indication and more beneficial over existing therapies [19].

PUMA can be granted for medicinal products that are not protected by SPC or SPC qualifying patents, and give the product a data exclusivity period of 8 years and a marketing exclusivity period of 10 years. This regulation is exclusivity for products that have been developed to be used in pediatric population.

Conclusion

Taking advantage of the multiple forms of market exclusivity available in both the United States and EU is critical for securing the optimum financial return on a new or updated drug. A pharmaceutical manufacturer can capitalize on these opportunities by considering the following recommendations:

A. Develop a comprehensive long term exclusivity strategy that incorporates the various testing and development activities required.

B. Plan Your Exclusivity Strategy Early

Considering the potential for a product's patent to expire before the product is introduced to market, a sponsor should assess early its optimal exclusivity strategy. It is essential for the innovator to familiarize itself with the numerous exclusivity options and to consider whether any such options are available for its Product (i.e., Is the product intended for an orphan population, is it safe for children, are there other indications for the product in the pipeline, is future OTC status a possibility). By preparing an exclusivity strategy early, a manufacturer can prepare for any steps necessary to attain additional forms of exclusivity, and can maximize its time in the market without competition.

C. Take advantage of U.S./EU Simplification Procedures

The orphan drug exclusivity common application suggests that there may be a trend toward EU/U.S. harmonization. Keeping abreast of any new developments, such as additional common exclusivity applications or mutual recognition policies, will save drug manufacturers both time and money.

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