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ARTICLE

REGULATORY EXCLUSIVITY IN THE UNITED STATES AND EUROPEAN UNION AND ITS IMPACT ON GENERIC ENTRY

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Abstract

Regulatory exclusivity is one of strategy apart from an intellectual property rights to get profit and return on investment done by the pharmaceutical industry on development of drugs. The reason of introducing regulatory exclusivity for drug products was that a lot of time would lost during approval of drug product and because of that at the time of approval of drug very little patent protection available to that drug. Pharmaceutical companies usually file patent application at respective countries at the time of an invention related to drug and it will take time more than 10 years to get approval from the authorities (FDA- Food and Drug Authority or EMEA-European Medicines Agency) and that leaves the patent holder with a much lesser duration, and sometimes none, to actually avail a return on the huge investment in R&D.

Key words: Regulatory exclusivity, Generic, Patent, Data Exclusivity, Market Exclusivity, New Chemical Entity Exclusivity, Clinical Investigation Exclusivity, Orphan Drug Exclusivity, Pediatric Exclusivity

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1. Introduction

Development of pharmaceutical medicine is an expensive process and approval from drug authority takes a lot of time because of this time consuming process very often patents protection related to pharmaceutical medicine are expired before approval or launch of medicines in the market. As a result, most pharmaceutical industries rely on the exclusivity granted under the FDA- Food and Drug Authority or EMEA-European Medicines Agency.

Regulatory exclusivity is exclusive marketing rights granted by FDA or EMEA upon approval of a drug. It may run simultaneously with a patent protection or not. It prevents submission or final approval of ANDAs or 505(b)(2) applications and therefore it is design in such way to balance between new drug innovation and generic drug competition.

Pharmaceutical companies generally file patent application in respective countries at the time of innovation of product. Approval of product will take almost 10 years or more from respective drug authority. This is because the requirement of conducting clinical trials to prove safety and efficacy of any new drug molecule is very tedious, costly and without any guarantee of favourable results. At the time of launch of product in a market, patent protection left on the product is very little. To provide pharmaceutical companies chance to recoup their investment on drug research & development and to give incentive to do an innovation, the FDA or EMEA have provided regulatory exclusivities to extend the period in which companies can market their products without any competition from generics companies.

This article is intended to provide an overview of the regulatory exclusivity provisions in the United States and European Union that pharmaceutical companies should consider while making strategy for global launch of their products and to maximize market protection of their products.

2. The United States Overview

The Hatch-Waxman Act of 1984 (The Drug Price Competition and Patent Term Restoration Act) introduced regulatory exclusivity in the United States. It provides up to five years market exclusivity to pharmaceutical companies introducing a new chemical entity to the market (NCE exclusivity), up to three years market exclusivity for conducting new clinical investigations (other than bioavailability studies) to support changes to drug products already on the market (Clinical Investigation or CI Exclusivity). Regulatory exclusivity attaches upon approval of a drug product if the statutory requirements are met. There is not any requirement to apply for these Hatch-Waxman exclusivities.

The Orphan Drug Act of 1983 provides up to seven years market exclusivity to drugs that treat diseases or conditions that affect

200,000 or fewer individuals in the United States. In addition to, The Best Pharmaceuticals for Children Act of 2002 provides 6 months market exclusivity which is attached to the other three exclusivities and the term of orange book listed patents itself.

A. New Chemical Entity Exclusivity (NCE)- 5 years

New chemical entity[1] means a drug that contains no active moiety that has been approved by FDA in any other NDA submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act. Active Moiety[2] is defined as any ion or molecule which is attributed to the drug's physiological or pharmacological action.

Since NCE exclusivity attaches to active moiety of drug, FDA cannot accept or approve generic applications of drug product contains same active moiety during the five year NCE exclusivity.[3]

For example: FDA has approved Erdafitinib on April 12, 2019. FDA has granted five years market exclusivity which is going to expire on April 12, 2023 because FDA has never approved other NDA which contains same active moiety as Erdafitinib has. Because of 5 years NCE exclusivity, FDA cannot accept any ANDA or 505(b)(2) application which contains same active moiety as Erdafitinib has until NCE expires or FDA can accept filing of ANDA or 505(b)(2) application which contains paragraph IV filing with respect to any one of orange book listed patents on NCE-1 year date. ANDA or 505(b)(2) applications can be filed after April 12, 2023 or If ANDA or 505(b)(2) applications contain paragraph IV certification with respect to at least one patent from orange book listed patents then they can be filed on April 12, 2022.

B. Clinical Investigation Exclusivity (CI)- 3 years

Pharmaceutical companies that conduct additional clinical trials on a previously-approved drug may be granted three additional years of Clinical Investigation Exclusivity[4]. Pharmaceutical companies may receive CI Exclusivity for the following changes: new dosage forms, new indications and a product's change from prescription to over-the-counter (OTC). In addition to, the clinical trials have to be new and do not have to rely on previously done clinical trials on approved drug. Unlike NCE exclusivity, ANDA or 505(b)(2) application can be filed during three years of CI exclusivity but they cannot be approved during period of CI exclusivity.[5] If generic applicants conduct own clinical trials to support approval of their application then FDA can approve their ANDA or 505(b)(2) during three years period of CI exclusivity.

C. Orphan Drug Exclusivity (ODE)- 7 years

To find a cure of rare or unusual conditions, pharmaceutical companies have to invest a lot of money and time as drug research and development cost are

really high. As patient population is very low for orphan diseases, the investment done by pharmaceutical companies to identify cure cannot be recovered even during normal exclusivity period. Therefore, FDA has given incentive of 7 years marketing exclusivity to recoup their investment. If drug product obtain seven years of orphan drug exclusivity then FDA can accept but not approve ANDA or 505(b)(2) application that contains same orphan indication during this period of exclusivity.[6] One more reason to provide longer exclusivity is to encourage pharmaceutical companies to do research on the areas where patient population is low, which otherwise get neglected and because of that the patient with such disease have to suffer a lot.

For example: Gefitinib (IRESSA) was approved by FDA on July 13, 2015 with seven years of ODE exclusivity which expires on July 13, 2022. Patent protection related to this product is expired but because of ODE, FDA cannot approve any generic version of IRESSA.

D. Pediatric Exclusivity (PED)- 6 additional months

Interaction of drug in children is different compare to adult. In order to encourage pediatric drug development and testing, congress had enacted The Best Pharmaceuticals for Children Act in 2002.[7] The act provides six additional months of exclusivity to pharmaceutical companies who conduct pediatric clinical trials on their approved and marketed drug product and generate information about the safety and efficacy of their drug product in children.

Pediatric exclusivity only attaches to orange book listed patents, NCE exclusivity, CI exclusivity and ODE exclusivity. Pediatric exclusivity runs after expiry of all other form of exclusivity. FDA generally initiate "written request"[8] to NDA applicant for a particular drug product. If NDA applicant conducts pediatric studies and submit to FDA in a response to "written request" from FDA then pediatric exclusivity will be granted to particular drug product. It is not necessary to have successful pediatric study to get pediatric exclusivity to particular drug product. There is only requirement of submission of pediatric studies to FDA in a response to "written request" is initiated by FDA. Pediatric exclusivity bar effective approval of ANDA and 505(b)(2) application.

Hypothetical case study: To understand it, consider a case where product is having NCE exclusivity expiring in Dec 2025, Orphan exclusivity for a particular indication out of multiple indication expiring in Dec 2027. The same product is also protected by product patent expiring in January 2025 and a formulation patent with specific excipient limitation expiring in Dec 2029. In such a scenario, generic player need to evaluate the blocking date before selection of product. In this case, product patent is expiring below NCE exclusivity and therefore NCE exclusivity

will be blocking instead of product patent. Formulation patent is having a specific excipient limitation, which can be easily design around; hence not considered as blocking. Orphan exclusivity will be blocking only for second indication for which orphan exclusivity is awarded but generic can market the product for first approved indication.

3. European Union overview

In 2005, the EU data exclusivity directive[9] was brought into force under which, pharmaceutical companies may receive up to 11 years of exclusivity for new drugs. In 2000, The EU orphan drug regulation[10] became effective and under which pharmaceutical companies may receive up to 12 years of exclusivity for orphan designated drugs.

A. EU Data Exclusivity "8+2+1"[11]

As per revised European Legislation, now new term of protection period is of '8+2+1' which is applicable only to new molecule entity for which the application for marketing authorisation approval has been submitted as of 30 October 2005 for MRP (Mutual Recognition Procedure), DCP (Decentralised Procedure) and national procedures and as of 20 November 2005 for centralised approval procedure.

Exclusivities of European Union which is now represented as "8+2+1" can be classified as 8 years of data exclusivity, 2 years of marketing exclusivity and additional 1 year of marketing exclusivity for approval of significant new indication if new indication approved during the first 8 years of authorisation. During first 8 years after the date of notification of the authorisation of the reference medicinal product to the Marketing Authorization Holder (MAH), no any generic or hybrid application can be filed or regulatory authority will not accept any generic or hybrid application during first 8 years. After 8 years, regulatory body will accept the generic or hybrid application, review it and provide approval after all regulatory requirements are complied. Under the provision of market exclusivity, generic or hybrid application holder cannot market their products before expiration of 10 years. Further 1 years of additional indication exclusivity will be applicable only if new indication has been approved during first 8 years and in that case, generic or hybrid applicant cannot market their product with that indication until expiry of that 1year exclusivity.

B. Orphan Drug Designation

Orphan drug designation[12] is typically for a disease category which his affecting less number of patient or a rare disease which is not commonly occurring. If any drug or medicine qualifies below criteria than it is eligible to be designated as orphan:

- Drug or medicine must be used for the treatment, prevention or diagnosis of a life-threatening disease and that prevalence of the disease in the EU must not be more than 5 in 10,000 or if drug is launched in the market then it

would generate insufficient return with respect to drug development cost.

- No satisfactory method of diagnosis, prevention or treatment of the disease is authorized in the European community or if a method exists, the drug or medicine must prove that it provides significant benefit than existing method.

Pharmaceutical companies must submit an application for orphan designation at any time prior to an application for marketing authorization. Committee for Orphan Medicinal Products (COMP) of EMA will examine the application for orphan designation. COMP must have to give its opinion within 90 days. Opinion of COMP sends to the European commission, which is responsible authority to grant orphan designation. As incentive, ten years of market exclusivity grants to orphan designated medicine by the European Union (EU).The marketing exclusivity for orphan drug can be extended by additional 2 years if pharmaceutical companies conduct specific studies in accordance with pediatric investigation plan.

The regulatory authority will not accept any generic or hybrid application and even an application to extend an existing marketing authorization until the expiry of orphan drug exclusivity that is 10 years. The authorised generic/hybrid product can only be placed on the market 10 or 12 years after expiry of the market exclusivity period applicable for the reference medicinal product.

In certain exceptional case, marketing authorisation may be granted, for the same therapeutic indication, to a similar medicinal product if:

a) consent is given by original orphan designation holder, or;

b) original orphan designation holder is not able to provide sufficient quantities of drug against the requirement of products in market, or;

c) the second application is safer, more effective or otherwise clinically superior in then the first orphan approved product.

C. Pediatric Exclusivity[13]

Pediatric exclusivity is awarded to encourage pharmaceutical companies to do clinical trials for pediatric populations. A pediatric investigation plan (PIP) is a designed and developed with aim of generating and creating data pool of clinical data in children to support an approval of medicine for children. Results of studies in children have to be included in all applications for marketing authorization for new medicines as per agreed PIP. This requirement also applicable even for a marketing authorisation holder (MAH) who wants to develop any new indication, pharmaceutical form or route of administration for an already approved pharmaceutical product and protected by intellectual property rights. Proposals by pharmaceutical companies should be

submitted for PIPs to the European medicines Agency's pediatric committee (PDCO). The committee is responsible for approval or refusal of the PIP. PDCO may grant PIP deferrals for some medicines in which an applicant can demonstrate its safety and efficacy in adults first and then can develop medicine in children. PDCO may also grants waiver for some medicines when there is no requirement to develop a medicine for children.

If pharmaceutical companies fulfil the requirement of pediatric investigation plan then applicants may benefit from following incentives:

- Product with marketing authorisation across the EU is eligible for six months of extension to their supplementary protection certificate (SPC). This extension is irrespective of the result of study means even if result is negative, six months extension is provided.
- If product is with Orphan designation, it is eligible for an additional two years of market exclusivity.
- If any drug is already approved for adult only, developing the same drug or medicine specifically for children that are already authorised but are not protected by a patent or supplementary protection certificate are eligible for a pediatric-use marketing authorisation (PUMA). If a product is approved under PUMA, such product will get 10-year period of market protection, including 8-year period of data exclusivity as an incentive.

Hypothetical case study: To understand it, consider a case where product is having Data exclusivity expiring in Dec 2025, Market exclusivity expiring in Dec 2027. The same product is also protected by product patent expiring in Jun 2028 and a formulation patent with specific excipient limitation expiring in Dec 2029. In such a scenario, generic player need to evaluate the blocking date before selection of product. In this case, product patent is expiring after Data exclusivity and Market exclusivity. Therefore Product patent blocking for market entry. Formulation patent is having a specific excipient limitation, which can be easily design around; hence not considered as blocking. However generic player can file dossier after expiry of Data exclusivity but can not market before expiry of Market exclusivity. Unlike in USA, here generic player will get approval though product patent is live and expiring in future.

4. Conclusion

It is very critical to understand the regulatory exclusivities available in the united states of America and European union to get optimum financial benefits and return of research and development cost associated with drug discovery and development. Pharmaceutical companies have to develop strategy as early as possible on regulatory exclusivities based on their intellectual property rights profile of their medicines. As early strategy

provide insight of timing of generic competition available in the markets, on that basis innovator can maximize its use of regulatory exclusivity by available additional exclusivity like CI exclusivity and pediatric exclusivity to further restrict generic competition in the markets. Hence understanding the regulatory exclusivity scenario along with patent scenario will help to take all business decisions like identification of product, starting of product development and evaluation of business case.

References:

1. See 21 CFR 314.108(a).
2. See 21 CFR 314.108
3. See 21 CFR 314.108(b)(2)
4. See 21 C.F.R. § 314.108
5. See 21 U.S.C. § 505(c)(3)(E)(iii),(iv)
6. See generally U.S.C. § 360aa-360dd; see also 21 C.F.R. Part 316.
7. Best Pharmaceuticals for Children Act of 2002 (BPCA), PUBLIC LAW 107–109
8. See https://www.fda.gov/drugs/development resources/written-requests-issued
9. Directive 2004/27/EC, amending Article 10 of Directive 2001/83/EC
10. Regulation (EC) No 141/2000 of the European Parliament

European Medicines Agency procedural advice for users of the centralised procedure for generic/hybrid applications EMEA/CHMP/225411/2006