# EXCLUSIVITY STRATEGIES OF INNOVATOR DRUG DEVELOPERS

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REVIEW ARTICLE

[1]**Chaitanya Prasad K***, [1]Prabodh M , [1]Ashish S, [1]Suthakaran R, [2]Naveen Reddy M, [3]Ravindra Reddy M

[1](Department of Pharmaceutical Management & Regulatory Affairs

Vijaya College of Pharmacy, Munaganoor (V), Hayathnagar (M), Hyderabad-501511, India

[2] Hetero Drugs, Hyderabad, India

[3] SIPRA Labs Limited, Hyderabad. India

***Corresponding Author's E-mail: chaitanyaprasadkolla@gmail.com*

**ABSTRACT**

Pharmaceutical drug development had become very costly and time consuming. There is an estimate that a drug from molecular development to marketing approvals cost $800 Millions. Drug approval process is time consuming process most companies loss their patent exclusivity before drug gets marketing approvals. To prevent innovators from monetary losses occurred in drug development and to encourage innovation US FDA and EMEA introduced exclusivities under various categories. Within the period of drug exclusivity no application is accepted either ANDA or 505 (b) (2).

**Keywords:** FDCA; EU; Exclusivity; FDA; EMEA; CDER; NDA; ANDA; Hatch Waxman Act.

## INTRODUCTION

Pharmaceutical development is a costly, time exhausting and uncertain process that takes years to accomplish. In many instances, patent protection expires before a new drug is approved for marketing. Most pharmaceutical firms in the United States and European Union (EU) depend on the exclusivity rights allotted under the U.S. Federal Food, Drug and Cosmetic Act (FDCA), and the corresponding EU authorities to recover their considerable investment in the drug research and marketing approval process. Hence, pharmaceutical companies must understand and use the different forms of non patent exclusivity in both the U.S. and EU in order to win in the global marketplace.

Pharmaceutical firms generally obtain patents on their products long before their product candidates are ready to enter market. Since it can take up to 12 years for a firm to obtain market approval, if any, patent protection left on the product at the time of commercializing. To provide pharmaceutical companies with a chance to recuperate their investment in drug research and development and to induce continuing innovation, the Food and Drug Administration (FDA) and the European Medicines Agency (EMEA) have enforced numerous provisions to increase the period during which companies can market their drugs free of generic market competition. These non-patent exclusivity provisions allow pharmaceutical organizations to market their products without competition from incoming generics, leading in significant financial profits for the original drug manufacturer.

## U.S. OVERVIEW

It is necessary that a pharmaceutical company assess its exclusivity options and develop its competitive strategy early in the drug development stages. In the United States, the FDCA provides several exclusivity provisions, including: 1) new chemical entity exclusivity 2) clinical investigation exclusivity 3) orphan drug exclusivity and 4) pediatric exclusivity.

As of recent FDCA amendments, drug makers now benefit from exclusivity periods that can be twice as long as they were 20 years ago, when pharmaceutical companies were required to depend almost exclusively on the drug product's patent term. The Drug Competition

 

and Patent Term Restoration Act (Hatch-Waxman Act) enacted in 1984, provides up to 5 years market exclusivity to companies introducing a new chemical entity to the market (NCE Exclusivity) and up to 3 years of market exclusivity for performing clinical trials to support changes to products already on the market (Clinical Investigation Exclusivity). Pharmaceutical firms are not required to apply for these Hatch-Waxman exclusivities.

The Center for Drug Research and Evaluation (CDER) determines the forms of exclusivity that are available for each new pharmaceutical product entering the market. Exclusivity may be conceded for Orphan Drugs to treat diseases that affect 200,000 or lesser individuals in the United States and for drugs that have undergone certain clinical testing in children.

**A. New Chemical Entity Exclusivity (1):**

A pharmaceutical manufacturer can obtain NCE Exclusivity in the United States by introducing a drug that contains an "active ingredient" that has not been antecedently approved by FDA in a new drug application (NDA). An "active ingredient" is defined as the compound responsible for the drug substance's physiological or pharmacological use.

Since the NCE Exclusivity attaches to the drug's active ingredient, FDA cannot approve or even accept abbreviated new drug application (ANDA) or 505(b)(2) application (that depends on investigations that were not performed by or for the 505(b)(2) applicant) for a generic that is based on the same active ingredient during the 5 year exclusivity period, no matter of whether the drug is proposed for the same indication as the innovative drug, or for another indication.

Since the approval process for an ANDA approximately two years and FDA cannot accept an ANDA for review during the period of NCE exclusivity, the duration of exclusivity from generic competition can exceed 7 years. New chemical entity exclusivity does not forbid FDA acceptance and approval of another NDA for a product with the same active ingredients that depends on clinical trials performed by or for the second New drug applicant.

**B. Clinical Investigation Exclusivity (2):**

Drug manufacturers that sponsor additional clinical testing on an antecedently approved drug that leads to changes in the marketed product pursuant to an approved new NDA or supplemental NDA may be granted 3 additional years of Clinical Investigation Exclusivity. Sponsors may obtain CI Exclusivity for the following alterations: new dosage forms, new indications and a product's shifting from prescription drug to over-the-counter (OTC). To support CI Exclusivity, the sponsor must conduct clinical trials (on human) that are: 1) new (not antecedently used to support approval of the product); 2) necessary to approval; 3) sponsored by the applicant 4) not a bioavailability study.

CI Exclusivity forbids FDA from approving a contender's ANDA or other application for the protected modification supported by the clinical trial. It does not prevent the approval of ANDAs for the original denotation. Unlike NCE Exclusivity, FDA can accept an ANDA and start the review during the CI Exclusivity period. However, FDA may not inform its approval of the contender's application until the duration of exclusivity is expired.

**C. Orphan Drug Exclusivity (3):**

The vast investment in time and money required to develop and receive approval of pharmaceutical products raised concerns that drug manufacturers would not spend the resources to develop products to treat rare or unusual conditions for which the market is limited, if such products were developed, their cost would be high. Federal Congress passed the Orphan Drug Act in 1983 to address this concern and induce innovation in this potentially underserved area. The Orphan Drug Act renders drug manufacturers with 7 years of market exclusivity period after FDA's approval of the drug, as well as research grants and tax reduction for each new orphan drug germinated. Orphan drugs are defined as those proposed to treat diseases affect 200,000 or fewer Americans, or for which the sales in the United States are not reasonably expected to

 

recover the drug manufacturer's cost of research and development for the new drug.

If a product is conceded orphan drug exclusivity, FDA may not approve (but may accept) applications for generic products that contain the same active ingredient and are labeled for the same orphan indication. FDA may accept and approve applications for drugs having the same active ingredient, for a different therapeutic indication.
FDA may accept and approve an orphan drug application for the "same drug" and the same orphan indication, If applicant proves that the drug product is "clinically higher-up" safer, efficient than the previous drug. This renders an incentive for pharmaceutical companies to continue to develop innovative and effective products for the orphan drug market.

**D. Pediatric Exclusivity (4):**

Historically, small drug testing was conducted in pediatric populations. Children may metabolize and react differently to specific drug products, the lack of pediatric data raised vexation among regulators, legislators. In order to address this vexation and encourage pediatric drug development and testing, Federal Congress enacted the Best Pharmaceuticals for Children Act in 2002. The Best Pharmaceuticals for Children Act allows 6 additional months of exclusivity (after all other exclusivities have expired) to drug manufacturers who conduct pediatric clinical trials on their marketed product and develop useful information about the safety and effectiveness of their product in pediatric population.

Pediatric exclusivity is applicable only to products that already have another form of marketing exclusivity. Therefore, innovator who obtains pediatric exclusivity will have its patent, NCE Exclusivity, Clinical Investigation Exclusivity, or orphan drug exclusivity extended by 6 months.
Pediatric exclusivity is granted to an innovator with an approved NDA for a drug, who conducts a pediatric study (ies) in reply to a written request from FDA for a study to evaluate the pediatric safety and efficacy of the drug. Pediatric exclusivity, once gained for a drug, applies not only to the specific drug product studied in the pediatric population, but to all of the applicant's dosages of drug, formulations and therapeutic indications for drugs with existing marketing exclusivity or patent life that contain the same active ingredient.
A pediatric study does not have to be successful for the pharmaceutical company to obtain pediatric exclusivity. The drug will be conceded 6 months of pediatric exclusivity, as long as the sponsor submits a study that reacts to FDA's requirements in its written request.

**EUROPEAN UNION OVERVIEW**

From the last few years, the EU has expanded significantly the chances for drug innovators to obtain market exclusivity for their products. Since 1993, European drug manufacturers have been able to obtain a supplementary protection certificate (SPC) to extend up to 5 years the patent for certain pharmaceutical products marketed in the EU in order to remunerate them for the prolonged time period required to obtain regulatory approval of these products.

In 2005, the EU Data Exclusivity Directive was come into force under which, manufacturers may receive up to 11 years of exclusivity for new drugs. The exclusivity awarded under the Directive may include 8 years of data exclusivity, 2 years of marketing exclusivity, and a potential 1 year extension.

**A. EU Data Exclusivity "8+2+1":**

Under the Data Exclusivity Directive, pharmaceutical companies may receive up to 11 years to market their product without any competition. These 11 years of exclusivity are consists of what the European Parliament has denoted an "8+2+1" exclusivity. Pharmaceutical company introducing its drug product to market in the EU can obtain 8 years of data exclusivity, 2 years of marketing exclusivity and a 1 year extension.

During the 8 period of data exclusivity competitors cannot submit generic applications for marketing approval. During this time, the innovator's data is considered as a trade secret

 

and new competitors cannot reference the data until the expiration of the 8 year data exclusivity period. A pharmaceutical firm that wishes to apply for marketing authorization approval within the data exclusivity period must conduct its own safety and toxicology studies, and its own clinical trials, without depending on the inventor's data.

After the 8 year data exclusivity period lasts, manufacturers of a "generic drug product" may depend on the data from the reference drug to demonstrate the generic's bioequivalence, necessary to obtain marketing approval. (5) During the 2 year period of marketing exclusivity, EU authorities cannot approve a marketing authorization application for the generic product. The initial marketing authorization applicant may obtain a one-year extension of marketing exclusivity if it obtains an additional authorization during the initial eight-year exclusivity period for one or more new therapeutic denotations that evidence significant clinical use over existing therapies. Within this span of time, marketing authorizations for a generic product cannot be approved.

**B. Orphan Drug Exclusivity (6):**

The European Orphan Drug Regulation, which was enacted on December 16, 1999 and came to existence on April 27, 2000, establishes incentives to encourage the R & D and marketing of orphan drugs. To obtain orphan drug exclusivity, 1) the drug must either be (a) proposed to diagnose, prevent, or treat a life-threatening or very serious condition affecting not more than 5 in 10,000 people in the EU (b) proposed to diagnose, prevent, or treat a life-ominous or very serious and chronic condition that, without incentives, and 2) there must not be any satisfactory method of treatment in the European Community, or if a method does exist, the medicinal product should be of important benefit to those affected by the condition.

The Orphan Drug Regulation allows a centralized procedure under which manufacturer may apply for orphan drug exclusivity. The manufacturer must submit an application for orphan designation at any time anterior to the application for marketing authorization application. European medical agency, through its Committee for Orphan Medicinal Products (COMP), is responsible authority for reviewing and approving orphan drug applications. COMP must furnish an opinion on the orphan drug designation within 90 days which, if acceptable, is then forwarded to the European Commission, which generally must decide within 30 days.

The advantages of orphan drug exclusivity in the EU are vast. If marketing authorization is approved pursuant to the EU's centralized procedure or by all Member States, the Community and the Member States will not accept for 10 years another application for a marketing approval, approve a marketing authorization or accept an application to prolong an existing marketing authorization, for the same therapeutic indication with respect to a similar pharmaceutical product.

**C. Pediatric Exclusivity (7):**

The Pediatric Regulations significantly varied the regulatory environment for pediatric pharmaceutical products. The Pediatric Regulations require applicants to include, in their marketing authorization application, data on their product's use in children resulting from an agreed-upon pediatric investigation plan (PIP). From January 26, 2009 applicants must include pediatric information in applications to extend an existing marketing authorization for pharmaceutical products protected by an SPC to include any new therapeutic indication, pharmaceutical dosage form or route of administration. Applicants may be exempted from the pediatric data requirements only if they receive a waiver.

**CONCLUSION**

United States FDA and European medicines agency have enforced numerous provisions to promote innovation by introducing exclusivity strategies which will exclude innovator from unnecessary competition from others. Within the exclusivity period no other application related to the drug product is accepted. In this span of time innovator will be the monopoly in

 

market and no other will compete with his product.

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## CONFLICT OF INTEREST

Author declares that there are no conflicts of interest.

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