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 non-patent exclusivity in both the U.S. and EU in order to succeed in the global marketplace.

Pharmaceutical companies generally obtain patents on their products or processes long before their product candidates are ready to go to market. Since it can take up to 12 years for a company to obtain market approval, there is often little, if any, patent protection left on the product at the time of marketing. To provide pharmaceutical companies with an opportunity to recoup their investment in drug research and development and to incentivize continuing innovation, the Food and Drug Administration (FDA) and the European Medicines Agency (EMEA) have implemented numerous provisions to extend the period during which companies can market their drugs free of generic competition. These non-patent exclusivity provisions allow pharmaceutical companies to market products without competition from incoming generics, resulting in significant financial benefits for the original drug manufacturer.

It is essential that a pharmaceutical company evaluate its exclusivity options and develop its competitive strategy early in the drug development process. In the United States, the

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FDCA provides several exclusivity opportunities, including: 1) new chemical entity exclusivity; 2) clinical investigation exclusivity; 3) orphan drug exclusivity; and 4) pediatric exclusivity. Similar forms of nonpatent exclusivity are available to pharmaceutical companies marketing drugs in the EU.

This article is intended to provide an overview of the nonpatent exclusivity provisions in the United States and EU that pharmaceutical companies should consider when forming a global exclusivity strategy for their products. In some instances, government authorities have established a common application for a specific form of exclusivity, reflecting the recent trend toward harmonizing and simplifying the process by which a drug manufacturer can attain exclusivity in the United States and EU.

I. U.S. Overview

As a result of recent FDCA amendments, drug manufacturers now benefit from exclusivity periods that can be twice as long as they were 20 years ago, when companies were required to rely almost exclusively on the drug product's patent term. The Drug Competition and Patent Term Restoration Act, or the Hatch-Waxman Act, passed in 1984, provides up to five years market exclusivity to companies introducing a new chemical entity to the market (NCE Exclusivity) and up to three years' market exclusivity for conducting clinical trials to support changes to products already on the market (Clinical Investigation or CI Exclusivity). Pharmaceutical companies are not required to apply for these Hatch-Waxman exclusivities.

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

A. New Chemical Entity Exclusivity

A pharmaceutical manufacturer can gain NCE Exclusivity in the United States by introducing a drug that contains an "active moiety" that has not been previously approved by FDA in a new drug application (NDA). An "active moiety" is defined as the molecule or ion responsible for the drug substance's physiological or pharmacological action.

Since the NCE Exclusivity attaches to the drug's active moiety, FDA cannot approve or even accept a competitor's abbreviated new drug application (ANDA) or 505(b)(2) application (that relies on investigations that were not conducted by or for the 505(b)(2) applicant) for a generic or follow-on product that is based on the same active moiety during the five-year exclusivity period, regardless of whether the drug is intended for the same indication as the original innovative drug, or for another indication.

Since the approval process for an ANDA averages approximately two years and FDA cannot accept an ANDA for review during the period of NCE exclusivity, the period of exclusivity from generic competition can exceed seven years. However, NCE exclusivity does not prevent FDA acceptance and approval of another NDA for a product with the same active moiety that relies on clinical trials conducted by or for the second NDA applicant.

B. Clinical Investigation Exclusivity

Drug companies that sponsor additional clinical testing on a previously-approved drug that leads to changes in the marketed product pursuant to an approved new NDA or supplemental NDA may be granted three additional years of Clinical Investigation Exclusivity. Sponsors 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). To support CI Exclusivity, the sponsor must conduct clinical (human) trials that are: 1) new (not previously used to support approval of the product); 2) essential to approval; 3) sponsored by the applicant; and 4) not a bioavailability study.

CI Exclusivity prevents FDA from approving a competitor's ANDA or other application for the protected modification supported by the clinical trial. It does not, however, prevent the submission or approval of ANDAs for the original indication. Unlike NCE Exclusivity, FDA can accept an ANDA and start the review process during the CI Exclusivity period. However, FDA may not deliver its approval of the competitor's application until the period of exclusivity is over. As with NCE Exclusivity, CI Exclusivity will not prevent FDA approval of a competitor's NDA that is supported by its own clinical trials.

C. Orphan Drug Exclusivity

The huge investment in time and money required to develop and obtain approval of pharmaceutical products raised concerns that drug companies would not expend the resources to develop products to treat rare or unusual conditions for which the market is limited or that, if such products were developed, their cost would be prohibitive. Congress passed the Orphan Drug Act in 1983 to address this concern and stimulate innovation in this potentially underserved area. The Orphan Drug Act provides drug

FDCA May/June 2009 Update 35
manufacturers with seven years of market exclusivity period after FDA’s approval of the drug, as well as research grants and tax credits for each new orphan drug developed. 19 Orphan drugs are defined as those intended to treat diseases and conditions that affect 200,000 or fewer Americans, or for which the sales in the United States are not reasonably expected to cover the drug manufacturer’s cost of research and development for the drug.19

If a product is granted orphan drug exclusivity, FDA may not approve (but may accept) applications for generic or second innovator products that contain the same active ingredient and are labeled for the same orphan indication.20 However, FDA may accept and approve applications for drugs having the same active moiety, for a different indication.21

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

D. Pediatric Exclusivity

Historically, little drug testing was conducted in pediatric populations. Since children may metabolize and respond differently to particular drug products, the lack of pediatric data raised concerns among regulators, legislators and practitioners. In order to address this concern and encourage pediatric drug development and testing, Congress enacted the Best Pharmaceuticals for Children Act in 2002.23 The Best Pharmaceuticals for Children Act grants six additional months of exclusivity (after all other forms of exclusivity have expired) to drug manufacturers who conduct pediatric clinical studies on their marketed product and develop useful information about the safety and effectiveness of their product in children.24

Pediatric exclusivity attaches only to products that already have another form of marketing exclusivity—the designation cannot stand on its own.25 Therefore, a sponsor who obtains pediatric exclusivity will have its patent, NCE Exclusivity, Clinical Investigation Exclusivity, or orphan drug exclusivity extended by six months.

Pediatric exclusivity is granted to a sponsor with an approved NDA for a particular drug, who conducts a pediatric study(ies) in response to a “written request” from FDA for a study to evaluate the pediatric effectiveness and safety of the drug.26 Pediatric exclusivity, once attained for a drug, applies not only to the specific drug product studied in the pediatric 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.27 A pediatric study does not have to be successful for the sponsor to obtain pediatric exclusivity.28 The drug will be awarded six months of pediatric exclusivity, as long as the sponsor submits a study that responds to FDA’s requirements in its “written request.”29

II. EU Overview

In the past few years, the EU has expanded significantly the opportunities for drug manufacturers to obtain market exclusivity for their products. Since 1993, European drug companies have been able to obtain a supplementary protection certificate (SPC) to extend for up to five years the patent for certain medicinal products marketed in the EU in order to compensate them for the lengthy time period required to obtain regulatory approval of these products.30

In accordance with Regulation (EEC) No 1768/92, an SPC will be granted only if, at the date of application, the product 1) is protected by patent; 2) is the subject of the first valid marketing authorization granted to market the product for a medicinal use; and 3) has not already been the subject of an SPC. The SPC comes into force only after the corresponding general patent expires for a period equal to 1) the period which elapsed between the date on which the patent application was filed and the date of the first marketing authorization, minus 2) five years. The SPC term may not exceed five years from the date on which it takes effect.

In 2005, the EU Data Exclusivity Directive31 was brought into force under which, sponsors may receive up to 11 years of exclusivity for new drugs. The exclusivity available under the Directive may include eight years of data exclusivity, two years of marketing exclusivity, and a potential one year extension.

In addition, under the EU Orphan drug regulations,32 which became effective in 2000, the Community and the Member States may not accept or grant for 10 years, a new marketing authorization, or an application to extend an existing marketing authorization, for the same therapeutic indication as an orphan drug. Finally, Regulation (EC) No 1901/2006 (Paediatric Regulation), which became
effective on January, 26, 2007, provides sponsors with the right to apply for a six month extension to the product’s SPC in return for conducting pediatric studies on the product.

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 risk of competition. These 11 years of exclusivity are comprised of what the European Parliament has termed an “8+2+1” regime.34 A drug company introducing its product to market in the EU can enjoy eight years of data exclusivity, two years of marketing exclusivity and a one year extension.35

During the eight-year period of data exclusivity competitors cannot submit generic applications for marketing authorization. During this time, the innovator’s data is treated as a trade secret and new entrants cannot reference the data until the expiration of the eight-year data exclusivity period. A company that wishes to apply for marketing approval within the data exclusivity period must perform its own safety and toxicology studies, and its own clinical trials, without dependence on the inventor’s data.36

The Data Exclusivity Directive includes a proviso that patent laws in EU member states should not prevent sponsors from conducting the studies and trials necessary to obtain marketing authorizations for the generic products, and the necessary consequential requirements.37 Although the scope and effect of this provision are not entirely clear, it appears to permit generic companies to undertake the studies necessary to obtain marketing authorization.

After the eight-year data exclusivity period ends, manufacturers of a “generic medicinal product” may rely on the data from the reference drug to demonstrate the generic’s bioequivalence, necessary to gain marketing approval.38 However, during the two-year period of marketing exclusivity, EU authorities cannot approve a marketing authorization for the generic product. Moreover, the initial marketing authorization holder 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 indications that demonstrate significant clinical benefit over existing therapies.39 During this time, marketing authorizations for a generic product cannot be approved.

B. Orphan Drug Designation

The EU Orphan Drug Regulation,40 which was adopted on December 16, 1999 and became effective on April 27, 2000, establishes incentives to encourage the research, development and marketing of orphan drugs.

To obtain orphan drug designation, 1) the drug must either be (a) intended to diagnose, prevent, or treat a life-threatening or very serious condition afflicting no more than five in 10,000 people in the EU; or (b) intended to diagnose, prevent, or treat a life-threatening or very serious and chronic condition that, without incentives, would probably not be marketed given its low likelihood that the marketing would generate sufficient return to justify the investment; and 2) 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.41

The Orphan Drug Regulation establishes a centralized procedure under which sponsors may apply for orphan drug designation. The sponsor must submit an application for orphan designation at any time prior to the application for marketing authorization. EMEA, through its Committee for Orphan Medicinal Products (COMP), is responsible for reviewing and granting orphan drug applications. COMP must provide an opinion on the orphan drug designation within 90 days which, if favorable, is then forwarded to the European Commission, which generally must adopt the decision within 30 days.42

The benefits of orphan drug designation in the EU are vast. If marketing authorization is granted pursuant to the EU’s centralized procedure or by all Member States, the Community and the Member States will not, for 10 years, accept another application for a marketing authorization, grant a marketing authorization or accept an application to extend an existing marketing authorization, for the same therapeutic indication with respect to a similar medicinal product.43

Regulation No. 847/2000 and recent guidance interpret the term “similar medicinal products” as those products with the same active substance or the same principal molecular structural features (but not necessarily all of the same molecular structural features), which acts via the same mechanism as the substances in the currently authorized orphan product, and which has the same therapeutic indication.44

Although market exclusivity for orphan drugs is generally granted for a period of 10 years, it may be extended to 12 years for pediatric products, or may be reduced to six years if, at the
end of the fifth year of exclusivity, the drug no longer satisfies the original designation criteria (e.g., there is sufficient evidence that the product is profitable enough to not justify maintenance of product exclusivity). In addition, the sponsor may lose its exclusivity if it consents to a second orphan drug application or is unable to supply enough of the drug in question. In addition, a second applicant can obtain marketing approval if it can demonstrate that its drug, “although similar … is safer, more effective or otherwise clinically superior” as compared to the initial orphan drug.

Additional benefits of orphan drug designation include access to advice from the EMEA on what is needed to achieve marketing approval, a centralized mechanism under which sponsors may obtain marketing approval, and a reduction or waiver of fees for marketing authorization.

B. Pediatric Exclusivity
The Paediatric Regulations significantly changed the regulatory environment for pediatric medicines. The Paediatric 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). In addition, as of January 26, 2009, applicants must include pediatric data in applications to vary or extend an existing marketing authorization for drug products protected by or eligible for an SPC to include any new indication, pharmaceutical form, or route of administration. Applicants may be excused from the pediatric data requirements only if they receive a waiver or a deferral.

Sponsors that include data from the PIP in their marketing approval applications or in applications to vary or extend an existing marketing approval for a product that is authorized in all Member States may apply for a six-month extension to the product’s SPC. This extension will apply, not only to the product’s pediatric indication, but to all indications of the product having the same active ingredient. The SPC term extension will not be available if a sponsor applies for, and obtains, a one-year extension of the products’ marketing protection “on the grounds that the new pediatric indication brings a significant clinical benefit in comparison with existing therapies.”

The Paediatric Regulation also creates a new type of marketing authorization, the Paediatric Use Marketing Authorization (PUMA), for medicinal products not protected by SPC or SPC qualifying patents. PUMAs may provide eight years of data exclusivity and 10 years marketing exclusivity for those products developed exclusively for use in the pediatric population.

III. Recent Efforts Toward U.S./EU Harmonization
As a result of the increasing similarity of the U.S. and EU exclusivity standards, and the trend for drug innovators to introduce their products in both markets, there have been efforts to simplify the dual exclusivity process. In late 2007, the United States and EU consolidated their orphan drug market approval requests into a single application, although each regulatory body continues to independently review the common application.

The decision to adopt a single orphan drug application reflects a larger initiative between the Commission, FDA and EMEA to minimize costs to the pharmaceutical industry and simplify the approval process, and drug manufacturers have presented numerous additional “areas for simplification” of the marketing authorization processes for consideration.

IV. Conclusion: Recommendations
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. △

2 See Relman, Arnold S. and Angell, Marcia, "America’s Other Drug Problem, The New Republic," (Dec. 16, 2002). The length of patent protection was previously 17 years from the date of the patent grant, but clinical trials and FDA approval often took up nine of these years. Since June 8, 1995, patent terms extend up to 20 years from the filing date of the earliest patent application. Available at www.uspto.gov/go/taf/patdesc.htm.
4 See id.
5 See id.
7 21 C.F.R. § 314.108 (a).
8 21 C.F.R. § 314.108 (b).
10 See id.
11 See 21 C.F.R. § 314.108.
12 See id.
13 See id.
15 See id.
16 See id.
19 See 21 U.S.C. 360bb, see also 21 C.F.R. Part 316.
21 See id.
22 See id.
24 See id.
25 See id.
26 See id.
28 See id.
29 See id.
33 See Ashurst, (Dec. 2005), Life Sciences and Regulatory Update: EU v. US generic pharmaceuticals regulation.
35 See id. (B).
36 See id. (B).
38 See id. (B), See also Drouault-Gardrat, supra note 26.
39 See revised Article 10(1) of Directive 2004/27/EC.
41 Guidance on aspects of the application of Article 8(2) of Regulation (EC) No 141/2000: Review of the period of market exclusivity of orphan medicinal products; See id.; See also Jenkins, supra note 34.
43 See Article 8(1) of Regulation No. 141/2000.
44 Regulation No. 847/2000 of April 27, 2000; see also Communication from the Commission, Guidance on aspects of the application of Article 8(1) and (3) of Regulation (EC) No 141/2000: Assessing similarity of medicinal products versus authorized orphan medicinal products benefiting from market exclusivity and applying derogations from that market exclusivity. (19 Sept. 2008).
47 See Jenkins, supra note 34.
49 See id.
51 See id.
52 See id.