



REGULATORY EXCLUSIVITY STRATEGIES: FURTHER PROTECTION FOR PHARMACEUTICALS IN US, EUROPE AND CANADA

Ravi Mistry¹,
Dilip Maheshwari*²

¹Department of Quality Assurance and Pharm Regulatory Affairs, L. J. Institute of Pharmacy, Ahmedabad, Gujarat 382210, India.

²Head of Department of Quality Assurance and Pharm Regulatory Affairs, L. J. Institute of Pharmacy, Ahmedabad, Gujarat 382210, India.

ABSTRACT

In order to provide a fair balance between the need for new pharmaceuticals and the need to provide medicine at a reasonable price to the general public, governments have put in place different mechanisms of protection and exclusivities. Though patenting is probably the oldest and most common form of protection, other forms of exclusivities exist. Regulatory exclusivities in the form of protection are especially suited to research-based pharmaceutical company's needs, while others are more in line with the needs of generic companies. Regulatory exclusivity is important in life-cycle management of different pharmaceuticals. This article discusses the use of alternative, non-patent forms of protection, otherwise known as marketing exclusivity and data protection or data exclusivity. This article defines and establishes the span of such protections in different jurisdictions, including the US, Europe and Canada, by analyzing the various existing regulations. Through regulatory exclusivity strategies, pharmaceutical stakeholders be aware of, fully understand, and properly use these additional forms of protection to maximize their return on investment.

Keywords: Exclusivity, Hatch-Waxman Act, Data Exclusivity, Market Exclusivity

INTRODUCTION

The discovery of vaccines, antibiotics, hormones such as insulin and, more recently, biotechnology products have saved millions of lives throughout the world. Products stemming from pharmaceutical research are also responsible for enhancing quality of life by providing treatments for, among other ailments, headache, pain, depression, high blood pressure, and high cholesterol. The pharmaceutical industry, which produces pharmaceuticals, is composed of two main groups: the research-based pharmaceutical companies (innovators) and the generic companies. While the former discovers and develops new medicines, the latter replicates, manufactures, and distributes lower-cost "copies" that are bioequivalent or biosimilar to the innovative product. In order to achieve a balance between the need for new pharmaceuticals and the need to provide such pharmaceuticals at a reasonable price, several governments have put in place different mechanisms of protection and exclusivities.

Address for correspondence

Dr. Dilip Maheshwari*

Head of Department of Quality Assurance and Pharm Regulatory Affairs, L. J. Institute of Pharmacy, Ahmedabad.
Email: dgmaheshwari@gmail.com

While patents are probably the oldest and most known form of protection,^[1] other forms of exclusivities exist. Alternative non-patent protections, otherwise known as marketing exclusivities, data protection or data exclusivity and patent term extensions have been created to address unsatisfactory situations in which existing incentives are not sufficient. While a marketing exclusivity will prevent a generic applicant from accessing the market with a "copy" of an original drug for a given term, data exclusivity defines a period of time during which the generic applicant is restricted from applying to the health authorities for market authorization. One or both exclusivities can apply. A patent extension, for its part, will lengthen a patent protection.

Given the increasing complexity and costs associated with drug development,^[2] it is important for pharmaceutical stakeholders to be fully aware of, and to properly use, non-patent alternative forms of protection. It is essential that the fullest extent of available protection be used during a pharmaceutical's life-cycle management to recover and profit from huge and growing research and development investment in new drugs. Given the lengthy and complicated regulatory approval process for drugs, non-patent alternative forms of protection compensate to some extent for the time lost during that approval process.

This article provides an overview of the various forms of protection available for pharmaceuticals in addition to or in replacement of patents. While some of these forms of protection are patent-based, others can be defined as supplemental, non-patent-based protections. This article discusses the span of such exclusivities and other forms of protection in different jurisdictions, including the United States, Europe and Japan, by analyzing the various existing regulations.

REGULATORY EXCLUSIVITY

A Drug will have two forms of market protection. The first comes in the form of “exclusivity” which is a creation of law. Exclusivity enables the drug product to have exclusive, or monopoly, status in the market for a certain number of years (for example, five years for a new chemical entity and other periods of time for different situations). Exclusivity means that any Regulatory Authority cannot legally approve a generic drug application for that product until the exclusivity period expires. Exclusivity should not be confused with patent protection, which is the second form of market protection for a marketed branded drug.^[3]

Types of regulatory exclusivity

There are mainly two types of drug regulatory exclusivity:^[4]

- A) Data exclusivity
- B) Market exclusivity

A) Data Exclusivity:

Data exclusivity refers to a set period of time after the marketing approval, during which no one else may rely on or use the innovator’s data to obtain a marketing authorization for a particular product. It constitutes an important incentive to the research and development of new medicines. Health authorities require, as part of a submission for a marketing authorization, that proprietary information be disclosed in order to ensure public health and patient safety. The innovator assumes the entire risk for the generation of the data, what requires expensive and lengthy clinical trials. Data Exclusivity is necessary to provide a measure of certainty to the innovator that they will be provided with a period of protection for their efforts of testing a drug. Patents and data exclusivity are different concepts, protect different subject matter, arise from different efforts, and have different legal effects over different time periods.^[5]

International obligations in relation to data exclusivity:

The most important international agreement dealing with the use of data submitted for regulatory approval is the World Trade Organization’s Agreement on Trade Related aspects of Intellectual Property rights (TRIPS).

Article 39.3 of TRIPS obliges countries to protect against unfair commercial use of confidential data on new chemical entities submitted by companies to obtain approval for marketing new drugs from a regulatory agency. Article 39.3 is important because TRIPS obligations are linked to the trade advantages which flow from WTO membership. A WTO member who fails to comply with TRIPS may lose those trade advantages. This creates a powerful economic incentive to comply. Consequently, almost all WTO member states have enacted legislation in response to TRIPS.^[6]

B) Market Exclusivity:

Market exclusivity is the period during which a new drug is protected from direct competition from generics. It is therefore important for originator companies to try to maximize this period in order to recuperate their research and development costs. While a marketing exclusivity will prevent a generic applicant from accessing the market with a “copy” of an original drug for a given term, data exclusivity defines a period of time during which the generic applicant is restricted from applying to the health authorities for market authorization. One or both exclusivities can apply.

For example, In the US, the FDA grants marketing exclusivity for each newly approved drug or formulation as follow: New chemical entity (NCE) for 5 years, orphan drugs exclusivity for 7 years. Policymakers from academia, industry, and government have called for federal initiatives to stimulate drug development. Most proposals target the intellectual property environment, because market-exclusivity periods, usually supported by patents, foster revenue generation in the pharmaceutical market. For example, longer market exclusivity has been recommended for “first-in-class” products and for newly approved drugs. Such incentives are politically attractive because they offer support for drug innovation without direct allocation of taxpayer funds. Yet patients (or their insurers) bear the costs by paying higher prices for the products during market-exclusivity periods. These programs may also be subject to misuse if they are implemented in a way that permits the incentives to be earned for marginal innovations or in contexts beyond the intended scope of the legislation.

Finally, hidden costs can emerge, such as the public health implications if market exclusivity makes essential drugs prohibitively expensive. This analysis critically reviews the origins and effects of three important pieces of legislation that support market-exclusivity incentive programs in pharmaceutical research and development. Although use of market-exclusivity incentives to promote pharmaceutical innovation has potential benefits, future legislative efforts aimed at encouraging investment in drug research and development should be more precisely designed to avoid waste and misuse, and they should be linked to demonstration of positive public health outcomes.^[7]

**Table 1: Federal Legislative Programs Using Market-Exclusivity Incentives to Promote
Pharmaceutical Research and Development**

Legislation	Year	Intended Effect	Potential Collateral Effects with Important Public Health Implications
Drug Price Competition and Patent Term Restoration Act (Waxman–Hatch)	1984	Increase the market-exclusivity period for brand-name drugs Increase the number of generic drug manufacturers challenging weak patents on brand name drugs	Allows the generic exclusivity incentive to be used to arrange settlements between generic and brand-name manufacturers that delay the market entry of viable lower-cost drugs
Prescription Drug User Fee Act	1992	Increase the market-exclusivity period for brand-name drugs by reducing the FDA review period	Results in the approval of drugs with important safety concerns in order to meet the accelerated review deadline Encourages the financial dependence of the FDA on the pharmaceutical industry, which may influence regulatory behavior
FDA Modernization Act, Section 111 (Pediatric exclusivity extension)	1997	Increase the number of studies of approved drug products in pediatric patients	Leads manufacturers that want the incentive to support poor-quality studies that do not have substantial effects on public health

Importance of Drug Regulatory Exclusivity:

1. 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.
2. As a result, most pharmaceutical companies in the United States, European Union (EU) and Japan depend on the exclusivity rights granted under the U.S. Federal Food, Drug and Cosmetic Act (FDCA), the corresponding EU and Japan authorities to recoup their considerable investment in the drug development and approval process. Pharmaceutical companies must understand and employ the different forms of non-patent exclusivity in the U.S., EU and Japan in order to succeed in the global marketplace.
3. 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.
4. 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), the European Medicines Agency (EMA) and the Pharmaceuticals and medical devices agency, Japan (PMDA) have implemented numerous provisions to extend the period during which companies can market their drugs free of generic competition.
5. 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.
6. It is essential that a pharmaceutical company evaluate its exclusivity options and develop its competitive strategy early in the drug development process.
7. In the United States, the FDCA provides several exclusivity opportunities, including: 1) New chemical entity exclusivity; 2) Clinical investigation exclusivity; 3) Generic drug exclusivity; 4) Orphan drug exclusivity; 5) Veterinary drug exclusivity; and 6) Pediatric exclusivity.
8. Similar forms of non-patent exclusivity are available to pharmaceutical companies marketing drugs in the European Union and Japan.^[8,9]

EXCLUSIVITY STRATEGIES IN USA

The United States is the world’s largest market for pharmaceuticals. Understandably, this country provides the largest number of drug-related exclusivities of any industrialized country. Most types of exclusivities are

available to innovators, while some are reserved for generic companies. In US, Regulatory exclusivities are rooted in the amendments to the Federal Food, Drug, and Cosmetic Act,^[10] commonly referred to as the Hatch-Waxman Act, passed by Congress in 1984. With these amendments, the U.S. government tried to reach a compromise between research-based pharmaceutical companies and generic companies.

A. Exclusivity Strategies for Innovators

I. 30-Month Stay Under the Hatch-Waxman Act

Under the Federal Food, Drug, and Cosmetic Act, all drug products sold in the United States must be approved on the basis of safety and effectiveness by the Food and Drug Administration (FDA). Those approved drugs are identified in Approved Drug Products with Therapeutic Equivalence Evaluations, a publication commonly known as the Orange Book.^[11] The Orange Book is an important resource for innovators because it provides patent information about the drugs it lists, which can be used to delay the approval of generic versions of these drugs. To obtain the rights to sell and market a new pharmaceutical, a drug sponsor must submit a new drug application (NDA). Within 30 days of approval of an application, patent information for purposes of listing in the Orange Book must be submitted to the FDA. The patents the FDA regards as being covered by the statutory provisions for submission of patent information are:

- (1) Patents that claim the active ingredient(s);
- (2) Drug product patents which include formulation/composition patents;
- (3) Use patents for a particular approved indication or method of using the product; and
- (4) Certain other patents as detailed on FDA Form 3542^[12]—that is, an approved supplement to change the formulation, an approved supplement to change the strength, or any other patented changes regarding the drug or patented changes for patents issued after drug approval.

A company wishing to market a generic version of a listed drug must file an abbreviated new drug application (ANDA). The ANDA must demonstrate that the proposed product is bioequivalent to an already approved reference listed drug (RLD) in the Orange Book. The ANDA must also comprise one of the four following certifications:^[13]

1. There is no patent information listed;
2. There is a listed patent, but it has expired;
3. The listed patent will expire on a stated date; or
4. The patent is invalid or will not be infringed.

If the ANDA filer makes a paragraph IV certification,^[14] the patent holder has 45 days to file suit for patent infringement; otherwise, the FDA will approve the generic product. If a suit is filed, the FDA cannot issue an ANDA to the generic company for a 30-month period. However, the FDA will be free to approve the ANDA in less than 30 months if the court rules the patent is invalid

and unenforceable or not infringed. On the other hand, the delay may also be lengthened if the court considers it necessary. It is therefore critical for patent holders to list their drug-related patents in the Orange Book because such listing can provide an additional barrier to generic entry.

II. New Chemical Entity Exclusivity

The new chemical entity (NCE) exclusivity is granted to any new drug containing a new chemical entity.^[15] The NCE offers five years of marketing and data exclusivity from the date of the drug's approval. The marketing exclusivity prevents the FDA from approving an ANDA containing the same NCE for the same approved use for five years. The FDA may, however, approve an NDA for the drug product. The data exclusivity prevents the FDA from accepting the filing of an ANDA until the end of the 5th year unless a patent is listed in the Orange Book; in such case, the FDA will accept the filing one year earlier. In the latter case, the end results are advantageous for the patentee because approval of an ANDA typically takes about 18 months.^[16] This protection applies only to the first approval of a drug product in the United States that does not contain an active moiety that has been previously approved by the FDA. The regulation defines active moiety as the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other non-covalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance.^[17] The NCE exclusivity will not be granted for new drug products with the same active moiety as a previously approved drug product even though the form or the use is new. For example, all esters or salt forms of a given compound are held to be equivalent active moieties and are not admissible to NCE exclusivity.^[18] However, an enantiomer can qualify as an NCE and be granted the exclusivity under strict conditions.^[19]

III. Orphan Drug Exclusivity

The orphan drug exclusivity provides the sponsor of an orphan drug a seven-year marketing exclusivity period.^[20] The orphan drug exclusivity is awarded only to drugs intended for treatment of a "rare disease or condition" (that is, affecting less than 200,000 individuals in the United States) or in instances where there is no reasonable expectation of recovering development costs of such a drug in the United States.^[21] If two sponsors are pursuing the same drug for the same medical indication, the first one to be approved will obtain the exclusivity. The orphan drug exclusivity prevents the FDA from approving a third-party NDA,^[22] a biologic license application (BLA),^[23] or an ANDA for the same drug used for the treatment of the same disease. Briefly stated, this exclusivity prevents FDA approval of the same active drug for the same medical indication. However, it will not block approval of the same drug for a different indication,

approval of a clinically superior drug, or approval of a drug with a greater safety profile. Furthermore, in contrast to NCE exclusivity, there is no restriction on filing an NDA or ANDA on the orphan drug before the expiration of the seven-year marketing exclusivity. In addition to marketing exclusivity, rewards such as research grants, ^[24] fee waivers ^[25] for regulatory approval, and tax credits may be provided through the Orphan Drug Act. In order to benefit from these tax incentives, the sponsor must have income from sales or royalties from commercial distribution of other products. In order to seek orphan-drug designation in the United States, each non-American sponsor must appoint a permanent resident of the United States as the sponsor's agent. ^[26]

IV. New Use or New Formulation Exclusivity (New Clinical Study Exclusivity)

This protection provides three years of marketing exclusivity for drug products that depend on new clinical investigations to support new therapeutic claims, even though they do not feature a new active ingredient. ^[27] This exclusivity is granted after successful submissions of results of new clinical investigations. It seeks to protect new formulations, new indications (even if same dosage), or other labelling changes of an old drug. Only changes implemented through an NDA or a supplement may benefit from the three-year exclusivity ^[28] and the three-year period starts from the date of approval from the NDA. Generic companies can also benefit from this protection if they submit their own data in support of their application. During the three years of exclusivity, the FDA will not approve an ANDA for the new use, although the ANDA can still be filed during that period. The FDA will also approve for the new use or formulation a new NDA during that period, although this scenario is unlikely because it would take longer than three years for anyone to prepare and file a new NDA. Once the protection expires, a pending generic application may be approved immediately.

V. Pediatric Exclusivity

The pediatric exclusivity adds a six-month marketing exclusivity to any existing exclusivity. ^[29] It operates as a general exclusivity extension added to the end of non-patent exclusivities and it adds six months to the life of patented drug products listed in the Orange Book containing the same active moiety. This additional six-month marketing exclusivity applies only to unexpired patents and exclusivities still in place at the time the pediatric exclusivity is granted. Because the exclusivity is awarded for a given active drug moiety, already approved related drug products containing the same active moiety will also be awarded the protection. Although patent protection is not extended, the FDA acts as if the exclusivity actually had a later expiration date and will not approve ANDAs until the extended date is met.

To be granted the pediatric exclusivity an applicant must successfully complete FDA-requested clinical trials of a drug product in a pediatric population. The clinical study has to be done in accordance with the instructions given by the FDA and the exclusivity will only be possible if the FDA makes the request for such studies in children. However, granting of the exclusivity is not dependent on the success of the study. Biological products that are subject to the Public Health Service Act are also eligible for pediatric exclusivity.

B. Exclusivities Strategies for Generic Companies

Because it is in the public interest to have access to affordable drugs, the U.S. government also created incentives for generic companies to help them bring copies of brand-name innovator's drugs to the market as soon as possible.

I. 180-Day Generic Product Exclusivity

Because it is not in the interest of the public to pay extra for drugs protected by weak or non-infringed patents, U.S. law provides a 180-day period exclusivity ^[30] to the first generic applicant who successfully challenges the enforceability of a listed patent. ^[31] During that exclusivity period no other generic version of the same drug product can be marketed. Being the first approved generic manufacturer able to compete for market share of a high-priced brand-name product may provide substantial economic benefits to that manufacturer. As a result, this exclusivity has now become the single most important motivator for the generic industry to challenge pharmaceutical patents. The 180-day period exclusivity is granted to the first generic manufacturer to file a substantially complete ANDA (that is, sufficient to permit review) for a drug product listed in the Orange Book. This same manufacturer must also challenge at least one of the patents listed for that drug product. In doing so, the applicant has to file a paragraph IV certification (that is, the patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the new generic drug ^[32]). This exclusivity will be granted to the first generic applicant who successfully challenges a listed patent. This exclusivity is only given to the same drug product—in other words, for the same drug with the same dosage form (for example, the FDA could approve an ANDA for a different dosage of the same drug).

C. Biosimilar Biological Products

Contrary to chemicals whose synthesis is generally well defined, highly controlled, and fully reproducible, the manufacture of biological products, such as recombinant proteins and monoclonal antibodies, is much more complex and challenging. Indeed, the biological activity, innocuity, and immunogenicity of biologicals may vary widely depending on the method of manufacture: the particular manufacturing methods and

conditions used many, for instance, affect the final three-dimensional conformation of a protein, change the glycosylation patterns of the protein, or yield the presence of undesirable cell culture artifacts in a final purified product. Thus, it is recognized that biological products are much more complex and expensive to develop and bring to market than conventional drugs. In order to encourage innovation and promote price competition in this field, the United States recently enacted a new legislation for biosimilar biological products (also referred as “follow-on-biologics” (FOB)). The Public Health Service Act (PHSA) ^[33] governs the licensing of biologics by reviewing biologic licence applications (BLA). The new Biologics Price Competition and Innovation Act of 2009 (BPCIA) ^[34] came into force on March 30, 2010 with the signature by President Obama of the Patent Protection and Affordable Care Act of 2010 (PPACA). ^[35] The BPCIA amended s. 351 of the PHSA (as well as s. 271(e) of the Patent Act), which establishes an abbreviated licensure pathway for biosimilar biological products, with provisions covering exclusivity periods and payment for biosimilars. The Act also created two pathways for follow-on-biologic approval: biosimilars (that is, a reference innovator product) and interchangeable. It is not within the scope of this article to disentangle this complex piece of legislation or to study all its ramifications in terms of FDA regulatory approval requirements, impact on patent prosecution strategies, or potential new litigation challenges. The following paragraphs focus on the newly available exclusivity provisions for innovators and generic companies and summarize their key features.

I. Exclusivity Period for Innovators

One of the key features of the BPCIA is that it grants 12 years of exclusive use to innovator manufacturers of reference biological products before biosimilars can be approved for marketing in the United States. ^[36] In addition, during the first 4 years, an application for a biosimilar product may not be submitted to FDA. The 4- and 12-year periods are determined from the date on which the reference product was first licensed under the Public Health Service Act (that is, the date of approval by the governmental authority that governs biologics). However, it is not clear whether the exclusivity provisions should be considered as “marketing exclusivity” or as “data exclusivity” and the 12-year period may actually soon be reduced to 7 years. The 4- and 12-year periods are further subject to an additional 6 months for pediatric studies requested by FDA. However, no exclusivity will be available for the “supplement for the biological product that is the reference product” or subsequent applications filed by the same sponsor or manufacturer of the reference product for such things as new indications, route of administration, and dosing schedule unless there is a change in the structure of the biological product that results in a change in safety, purity, or potency.

In addition, the BPCIA provides exclusivity for a reference biological product that has been designated for a rare disease or condition (that is, an orphan biological product). A biological product seeking approval for a disease or condition that is biosimilar to or interchangeable with such a reference product will not be licensed until the expiration of the later of:

- 7 years from the date of approval or issuance of a licence for the reference product; ^[37] and
- The 12-year period for the innovator biological product as described above. ^[38]

II. Exclusivity Period for Generics

The Patent Protection and Affordable Care Act of 2010 provides for exclusivity for the first product determined to be “interchangeable” with the pioneer reference biologic. Several scenarios are provided in the Act pursuant to which exclusivity would be calculated. Briefly, the FDA cannot consider a second or subsequent biological product to be interchangeable for any condition of use until the earliest of:

- 1 year after the first commercial marketing of the first approved interchangeable biosimilar biological product;
- 18 months after resolution of patent litigation—that is, final court decision, including appeal—against the first approved interchangeable biosimilar biological product or dismissal of the first approved interchangeable biosimilar biological product;
- 42 months after approval of the interchangeable biosimilar biological product if applicant sued and litigation is still ongoing; and
- 18 months after resolution after approval of the first interchangeable biosimilar biological product if the applicant that submitted that application has not been used.

EXCLUSIVITY STRATEGIES IN EUROPE

Initially, data exclusivity was not an issue in Europe. When marketing authorizations were required for generics from 1975, no legal frame work existed on data exclusivity. The Commission considered this problematic because unauthorized use of data “seriously penalizes the innovating firm which has had to meet the high cost of clinical trials and animal experiments, while its product can be copied at lower cost and sometimes within a very short period”. In 1984, DG Enterprise of the European Commission therefore put forward a proposal for ten years of data exclusivity, after which a second applicant could cross-refer to the same data. Subsequent negotiations resulted in Directive 87/21/EEC ^[39], which

provided a period of six years of data exclusivity for most pharmaceuticals starting at the date of first market authorization, and ten years for biotechnological and high-technology medicinal products. Member states were allowed to extend the period to ten years for all pharmaceuticals if they considered this “in the interest of public health”. Belgium, France, Germany, Italy, the Netherlands, Sweden, and the United Kingdom did so. Member states also had the option not to apply the six-year period beyond the date of patent expiry of the original product so that data exclusivity did not extend the twenty years of protection from free market competition. Denmark, Austria, Finland, Ireland, Luxembourg, Greece, Spain, and Portugal provided six years, with the latter three not offering data exclusivity beyond patent expiry. In 2001, DG Enterprise of the Commission put forward its proposal for harmonization of national differences in data exclusivity,^[40] which finally resulted in the adoption of Directive 2004/27/EC in March 2004.^[41] The final compromise resulted in the so-called “8 + 2 + 1” formula on data exclusivity. This implies eight years of data exclusivity and two additional years of market exclusivity for authorizations (thus, generics companies could start the necessary tests after the expiration of the data exclusivity period of eight years), plus one additional year of protection for new indications of original products. As well, one year data exclusivity for new indications for well-established substances and one year data exclusivity for changes from prescriptive to over-the-counter (OTC) status. In addition, the final outcome includes a Bolar provision (which had been in place in the United States since 1984) as well as a Eurogenerics and historical reference principle.

A. New Chemical Entity Exclusivity

For drugs submitted for authorization on November 1, 2005 and later, an EU directive provides for a total of 10 years of exclusivity for new chemical entity exclusivity (NCE) and up to 11 years if the new product is for treating a “significant new indication.” A revised directive introduced a harmonized “8+2+1” formula wherein: (1) an NCE will be entitled to eight years of data exclusivity; (2) two additional years of marketing exclusivity; and (3) one additional year of marketing exclusivity on approval of an improvement if it involves a “significant new indication.” The eight-year data exclusivity is given to the NCE beginning with its initial approval as a European medicinal product. A generic applicant can file a request for a marketing authorization after that eight-year period, but it will have to wait at least two more years before it can place its drug on the market. The two-year market exclusivity can be extended by an additional year if the authorization has been obtained during the first eight-year period for one or more new “significant” therapeutic indications.

B. Orphan Drugs

An orphan drug is a medicinal product “intended for the diagnosis, prevention or treatment of a life-threatening or

chronically debilitating condition”^[42] that affects no more than 5 people out of 10,000 in the European Union. This type of drug can be granted 10 years of marketing exclusivity from the date of approval. The Committee for Orphan Medicinal Products (COMP), created in 2000, is in charge of reviewing designation applications from companies intending to develop medicines for rare diseases. Furthermore, an additional 2 years of market exclusivity can be granted to pediatric orphan drugs (for a total of 12 years).^[43]

C. Pediatric Exclusivity

The European Union legislation provides an additional six-month extension to existing patent term extensions (SPCs) for patented pediatric drugs, similar to that offered in the United States. This patent term extension is an incentive for pharmaceutical companies to carry out dosage tests on pediatric populations.^[43] The Pediatric Committee of the EMEA is responsible for granting the extension, but it must first approve the results of a pediatric investigation plan (PIP). The six-month extension can only be granted if the application is filed at least six months before the expiry of the SPC term.

D. Over-the-Counter Drugs

Over-the-counter (OTC) drugs are medicinal products that can be bought without prescription—that is, they do not require direct supervision from a health specialist. In most countries, OTC drugs may be advertised anywhere, unlike prescription drugs, which can only be advertised to doctors. Because the EU governments do not reimburse patients for OTC drugs, one year of data exclusivity is granted for switches from a brand-name prescription drug to OTC status. In practice, this data exclusivity, in order to be granted, must be seen not only as relevant, but also as necessary (that is, it should not be granted for existing data).^[44] Furthermore, only the EMEA decides whether a drug product can be available by prescription or nonprescription and EU member countries still retain authority over distribution and subcategorization.^[45] Consequently, OTC drug reviews and approvals can take years to process.^[46]

E. Biosimilars

Since 2004, biosimilar medicinal products can follow an abridged procedure; they represent approximately 6 percent of all the pharmaceuticals currently marketed in Europe.^[47] Biosimilar medicinal products, also known as follow-on biologics, are approved by the European Commission on the basis of a positive scientific opinion issued by the EMEA. The company must therefore demonstrate the comparability of their product with the reference medicine with a high degree of certainty (comparability studies). This is evaluated on a case-by-case process. Directive 2001/83/EC gives the requirements for the marketing authorization applications (MAAs);^[48] in

this regard; the Committee for Medicinal Products for Human Use (CHMP) has issued specific guidelines.^[49]

EXCLUSIVITY STRATEGIES IN CANADA

The pharmaceutical sector is one of the most innovative and profitable industries in Canada. It is composed of brand-name drug companies and generic drug companies totaling more than 390 pharmaceutical and 400 biotech companies. Pharmaceutical sales in Canada have a three percent share of the global market, making Canada the 9th largest world market.^[50] Although the mechanisms of protection for new pharmaceuticals are much less extensive than in the United States, Canada is the only other country to have a statute similar to the 30-month stay under the U.S. Hatch-Waxman Act. There is no patent term extension available but developers of new chemical entities may benefit from a limited period of marketing and data exclusivity.

A. Patented Medicine (Notice of Compliance) Regulations

The Patented Medicines (Notice of Compliance) Regulations is a statute by which an innovator may prevent the minister of health from approving a generic drug for a period up to 24-months. The minister of health maintains a register of patents on medicines for which a notice of compliance (NOC) has been issued.^[51] According to the NOC process, which is similar in some respects to the U.S. 30-month stay, a generic producer who files an abbreviated new drug submission (ANDS) must address an innovator patent listed on the register before Health Canada issues a regulatory approval. The generic company may allege non-infringement of any listed patent, challenge the validity of concerned listed patents, or advise Health Canada that it will wait for the minister to issue the NOC when the patent expires. If there is a challenge regarding the validity or infringement of its patent, the innovator company will then have 45 days to apply to a court for an order prohibiting the minister from issuing the NOC. On being served with a notice by the patent owner of such an application to the court, the minister (Health Canada) is prohibited from issuing an NOC for a period of up to 24 months. During that time, the Court will review allegations of non-infringement and/or invalidity. The 24-month stay ceases to apply if the court rules that the patent is invalid or non-infringed, but it may be extended in certain circumstances if the court deems it necessary. In addition, drugs that have been withdrawn from the market will not benefit from this protection because the minister is required to delete any patent listed for such a drug. There are important considerations for patent holders who want to benefit from the 24-month stay. Notwithstanding the existence of a patent for the drug, it is a pre-requisite that the register list the relevant patent(s) to the drug product. The register must also be accurate and complete because the list of patents will be “frozen” as of the date the generic applicant files its ANDS and patents added later will not be considered. Finally, innovators must act

diligently upon issuance of their patent because they have only 30 days to list their patent on the register after grant of the patent or, if the patent has been issued already, they have to file a request to add the patent to the register when submitting an NOC.

B. Innovative Drugs

Data protection provisions for new drug products were first introduced in 1995.^[52] However, very narrow interpretations by the courts have quickly rendered these provisions ineffective in the protection of innovative drugs.^[53] On October 5, 2006, the Food and Drug Regulations were amended to allow innovators a period of marketing and data exclusivity. Under the amended Food and Drug Regulations, an innovative drug approved after June 17, 2006 can be granted an eight-year exclusivity protection consisting of six-years of data exclusivity plus two years of marketing exclusivity. The term “innovative drug” is defined as “a drug that contains a medicinal ingredient not previously approved in a drug by the Minister and that is not a variation of a previously approved medicinal ingredient such as a salt, ester, enantiomer, solvate or polymorph.” Therefore, previously approved drugs, new uses of an old drug, or new combination therapies of pre-existing drugs are not eligible for the exclusivity. However, the exclusivity would be applicable to combinations where one of the drugs is new. Some variations, such as metabolites or prodrugs, are evaluated on a case-by-case basis and may also be eligible. In order to benefit from this protection, the innovative drug must have received an NOC and be marketed in Canada. The six years of data exclusivity plus two years of marketing exclusivity means that a generic company is prohibited from filing an ANDS in Canada until six years after approval of the innovative drug. The generic company may file a drug submission within the six-year term, but under no circumstances will the generic company be granted approval before the expiration of the eight-year term. The eight-year term may also be the subject of a further six-month extension for pediatric studies. As expected, Canada’s Generic Pharmaceutical Association did not welcome these new provisions and the Association quickly decided, along with Apotex, to challenge the validity of the legislation in court, claiming that the legislation was ultra vires and without legal force and effect. It is only recently that the Federal Court of Appeal rendered a unanimous decision confirming the validity of the amended regulations.^[54]

C. Pediatric Exclusivity

The eight-year exclusivity for an “innovative drug” may be extended for a further six months where studies for use of the drug in pediatric populations are submitted. These studies must relate to clinical trials that were designed and conducted with the purpose of increasing knowledge about the use of the drug in pediatric populations.^[55] It must be clear that the goal of such studies was to increase knowledge about the use of the drug in pediatric populations. In order to benefit from the

six-month extension, the pediatric studies have to be submitted as part of the original drug application for the innovative drug or within the first five years of the eight-year term.

D. Subsequent-Entry Biologics

In Canada, “biosimilars” are referred to as subsequent-entry biologics (SEBs). The term “subsequent-entry-biologics” is defined as “a biologic product that is similar to and would enter the market subsequent to an approved innovator biologic product.” Biologic drug products are complex because, unlike pharmaceutical drugs, which are synthesized or purified using traditional chemical methods, biologics are produced by living matter such as micro-organisms or plant or animal cells. However, due to the considerable complexity of biologics, SEBs cannot be considered as perfect replicas. In other words, an SEB is not a “generic biologic” and it must be submitted to a distinct and rigorous approval process. Health Canada is working on a regulatory framework for SEBs and in 2010 issued a guidance document: “Guidance for Sponsors: Information and Submission Requirements for Subsequent Entry Biologics (SEBs).” Also in 2010, Health Canada updated its guidelines regarding NOC regulations and data protection. Although Health Canada will accept a reduced non-clinical and clinical package for SEBs, which is more or less an abbreviated submission package, the sponsor of a SEB must file a new drug submission in order to obtain a market approval. In addition, even if non-clinical and clinical data previously generated with the reference biologic drug product can be used for the SEB filing, a SEB itself cannot be used as a reference biologic drug for future SEB submissions.

Because they are not considered to be “innovative drugs,” SEBs cannot qualify for data protection. Furthermore, submission filings of SEBs are subject to regulatory restrictions about data protections awarded to another innovative product. To that effect, sponsors will not be able to file a drug submission for an SEB based on a direct or indirect comparison to an innovative drug until six years after the issuance of the NOC granted to that innovative drug. The sponsor must wait two more years after that six-year period in order to be granted its own NOC (for a total of eight years of exclusivity). Finally, SEBs are subject to s. 5 of the Patented Medicines (Notice of Compliance) if their filing “makes a direct or indirect comparison with, or reference to, another drug”—that is, either the notice of compliance will not be issued until expiration of the patent of the reference innovative product or the SEB manufacturer files a notice of allegation stating that the patent is invalid, improperly listed, or not infringed.^[56]

CONCLUSION

Prudent life-cycle management of pharmaceuticals involves not only securing protection through different patents for different inventions (for

example, molecules, polymorphs, salts, formulation, and new uses), but also the use of intellectual property protection to the fullest extent permitted by way of patent term extensions, marketing exclusivities, and data protections. Although patents are a pillar of any protection strategy for new drugs, data and market exclusivities supplement patent protection beyond its standard duration in order to compensate for time lost during the drug approval process. The United States and the European Union provide the greatest scope of non-patent exclusivity legislation, which have been implemented by the governments to stimulate innovation while allowing generic drug companies to offer competitively priced medicine to consumers. This situation probably explains why the European and North American pharmaceutical industries are so strong; history has shown that stronger protection has been a positive force for pharmaceutical innovation. Compared with the United States and the European Union, Canada’s regime is largely incomplete. Although we can find in the Canadian legislation some data and market exclusivities, these are generally of shorter term than their foreign counterparts. In addition, there is no exclusivity for orphan drugs. Canada also has the unenviable distinction of being the only G8 country not offering patent term restoration to compensate for the time lost in regulatory and governmental procedures. These shortcomings have been highlighted by many players in the pharmaceutical sector and other groups calling for a greater protection of innovation. Knowledge is power when it comes time to optimize and effectively coordinate the life-cycle management of a drug. Pharmaceutical stakeholders should be fully aware and properly use the alternative non-patent forms of protection discussed in this article, because a proactive approach that takes into consideration all available forms of protection should deliver substantive returns for years to come.

ACKNOWLEDGEMENTS

The authors are thankful to Dr. K. Pundarikakshudu, Director of L. J. Institute of Pharmacy, Ahmedabad, India for providing all the facilities and encouragements to carry out the work.

REFERENCES

1. Serge Lapointe, “L’histoire des brevets” (2000) 12 C.P.I. 633 at 633.
2. Christopher P. Adams and Van V. Brantner, “Estimating the Cost of New Drug Development: Is It Really \$802 Million?” (2006) 25:2 Health Affairs at 420: studies published since 2003 report that costs to bring a new drug to market generally vary from around \$500 million to \$2 billion.
3. Henry G “Regulatory Exclusivity” http://neeo.univgeneric_competition.
4. Ywe L, “Types of Regulatory Exclusivity” forum-americas.org/sites/default/files/documents/20120614

5. International Federation of Pharmaceutical Manufacturers & Associations, "Data Exclusivity" <http://www.ifpma.org/innovation>
6. Jonathan R, "International obligations in relation to data exclusivity" <http://www.findlaw.com.au/articles/1576/data-exclusivity-further-protection-for-pharmaceut.aspx>
7. Aaron K, "Marketing Exclusivity" <http://health.accel-it.it/assets/NEJM%202010,%20Kesselheim.pdf>
8. Chaitanya P, "Importance of Drug Regulatory Exclusivity" http://www.academia.edu/7439136/EXCLUSIVITY_STRATEGIES_OF_INNOVATOR_DRUG_DEVELOPERS_REVIEW_ARTICLE
9. John T, "Importance of Drug Regulatory Exclusivity" http://www.law.umaryland.edu/marshall/crsreports/crsdocuments/R42890_01072013.pdf
10. http://uscode.regstoday.com/21USC_CHAPTER_9.aspx#21USC301
11. The Orange book can be searched online: <<http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm>>.
12. FDA, Development & Approval Process (Drugs), online: <<http://www.fda.gov/drugs/developmentapprovalprocess/ucm079068.htm>>.
13. <http://www.gpo.gov/fdsys/pkg/USCODE-2010-title21/pdf/USCODE-2010-title21-chap9-subchapV-partA-sec355.pdf>
14. <http://www.gpo.gov/fdsys/pkg/USCODE-2010-title21/pdf/USCODE-2010-title21-chap9-subchapV-partA-sec355.pdf>
15. 21 USC §355(c)(3)(E)(ii), (j)(5)(F)(ii), (b)(2), (b)(1); Abbreviated New Drug Applications Regulations; New Drug Product Exclusivity, 21 CFR §314.108(b)(2).
16. Martin A. Voet, *The Generic Challenge, Understanding Patents, FDA & Pharmaceutical Life-Cycle Management*, 2d ed. (Boca Raton, FL: Brown Walker Press, 2008) at 109.
17. <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=314.108>
18. 21 CFR §314.108(a); Abbreviated New Drug Applications Regulations, Patent and Exclusivity Provisions.
19. Food and Drug Administration Amendments Act, 2007, Public Law 110-85 (27 September 2007), s. 505 of the FD&C Act (21 U.S.C. 355), as amended by s. 1113.
20. 21 USC §360aa-dd; 21 CFR §316.
21. 21 USC §360aa-dd (Orphan Drug Act); 21 CFR §316.31(a).
22. <http://www.gpo.gov/fdsys/pkg/USCODE-2010-title21/pdf/USCODE-2010-title21-chap9-subchapV-partA-sec355.pdf>
23. <http://www.gpo.gov/fdsys/pkg/USCODE-2010-title21/pdf/USCODE-2010-title21-chap9-subchapV-partA-sec355.pdf>
24. The FDA Office of Orphan Products Development (OOPD) administers two extramural grant programs, online: <<http://www.fda.gov/ForIndustry/DevelopingProduct/sforRareDiseasesConditions/default.htm>>. Other grants are also available. In total, 12 to 15 grants are awarded annually; see M.E. Haffner et al., "Two decades of orphan drug development" (2002) *Nature Rev. Drug Discovery* 1:821-5.
25. The fee exemptions are stipulated in the Food and Drug Administration Modernization Act (FDAMA) of 1997. See also Enrique Seoane-Vazquez et al., "Incentives for orphan drug research and development in the United States" (2008) *Orphanet Journal of Rare Diseases* 3:33.
26. <http://www.gpo.gov/fdsys/pkg/CFR-2012-title21-vol5/pdf/CFR-2012-title21-vol5-sec316-22.pdf>
27. 21 USC §355(c)(3)(E)(ii), (c)(3)(E)(iii), (c)(3)(E)(iv), (j)(5)(F)(ii), (j)(5)(D)(iii), (j)(5)(D)(iv), (b)(1), (b)(2); Abbreviated New Drug Applications Regulations; 21 CFR §314.108(a), (b)(4)(iv), (b)(5).
28. 21 CFR §314.
29. Food and Drug Administration Modernization Act (1997), 21 USC §355(a); for incentives see also, online: <<http://www.fda.gov/forindustry/developingproductsforrareDiseasesConditions/howtoapplyfororphanproductdesignations/ucm135125.htm>>.
30. <http://www.gpo.gov/fdsys/pkg/USCODE-2010-title21/pdf/USCODE-2010-title21-chap9-subchapV-partA-sec355.pdf>
31. 21 USC §355(j)(2)(A)(vii)(IV).
32. 21 USC §355(j)(2)(A)(vi)(IV).
33. <http://www.gpo.gov/fdsys/granule/USCODE-2010-title42/USCODE-2010-title42-chap6A-subchapII-partF-subpart1-sec262>
34. Patient Protection and Affordable Care Act of 2010, Pub. L. No. 111-148, §7001, 124 Stat. 119.
35. Patient Protection and Affordable Care Act of 2010, Pub. L. No. 111-148, 124 Stat. 119.
36. Patient Protection and Affordable Care Act of 2010, Pub. L. No. 111-148, §7002(a)(2), 124 Stat. 119 (Biologics Price Competition and Innovation Act of 2009).
37. 21 USC §360cc (a) (2) (Protection for Drugs for Rare Diseases or Conditions); FD&C Act, s. 527(a).
38. Patient Protection and Affordable Care Act of 2010, Pub. L. No. 111-148, §7002(a)(2), 124 Stat. 119 (Biologics Price Competition and Innovation Act of 2009), section amending s. 351(k)(7) of the PHSA.
39. Directives EC, Council Directive 87/21/EEC amending Directive 65/65/EEC (Approximation of Provisions Laid Down by Law, Regulations, or Administrative Action Relating to Proprietary Medicinal Products, [1986], O.J., L. 15/38 (22 December 1986).
40. Directives EC, Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community Code relating to medicinal products for human use, [2004] O.J., L. 311/67.

41. Europa, Summaries of EU Legislations, “Community Code relating to medicinal products for human use,” online: <http://europa.eu/legislation_summaries/internal_market/single_market_for_goods/pharmaceutical_and_cosmetic_products/121230_en.htm>.
42. Regulation EC, Regulation No. 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products, [1999] O.J., L. 18/1 at 3.1(a).
43. Regulations EC, Regulation No. 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for pediatric use and amending Regulation (EEC) No. 1768/92, Directive 2001/20/EC, Directive 2001/83/EC, and Regulation (EC) No. 726/2004, [2006] O.J., L. 378/1 at 37.
44. Melanie Senior, “European Switch Progresses, but Stronger Incentives Needed for OTC’s” EuroPharma Today (1 February 2010), online: EuroPharma Today <<http://www.euopharmatoday.com/2010/02/european-switch-progresses-but-stronger-incentives-needed-for-otcs-.html>>.
45. Christopher Morrison, “In Europe, Centralized OTC Switch Still Has a Few Bugs” EuroPharma Today (15 June 2009), online: EuroPharma Today <<http://www.euopharmatoday.com/2009/06/in-europe-centralized-otc-switch-still-has-a-few-bugs-.html>>.
46. Melanie Senior, “EU-Wide OTC Approvals Highlight the Drawbacks of National Processes” EuroPharma Today (11 February 2010), online: EuroPharma today <<http://www.euopharmatoday.com/2010/02/euwide-otc-approvals-highlight-the-drawbacks-of-national-processes-.html>>.
47. “Biosimilar Medicine FAQ” European Medicine Generic Association (September 2007), online: European Medicine Generic Association <<http://www.egagenerics.com/FAQ-biosimilars.htm>>.
48. Article 10(4) of Directive 2001/83/EC and Section 4, Part II, Annex I (as amended by Directive 2003/63/EC, O.J., L159, 27.6.2003 at 46 and Directive 2004/27/EC, O.J., L136, 30.4.2004 at 34).
49. “Guideline on Similar Biological Medicinal Products” European Medicines Agency (30 October 2005), online: <http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003517.pdf>.
50. See Government of Canada, online: <<http://investincanada.gc.ca>> and Industry Canada, online: <<http://www.ic.gc.ca>>.
51. The Patent Register can be consulted online: <<http://www.patentregister.ca>>.
52. *Supra* note 50, s. 7(5)(b).
53. *Food and Drug Regulation*, C.R.C., c. 870, s. C.08.004.1.
54. *Apotex Inc. v. Canada (Health)*, 2010 FCA 334. See also Mathieu Gagné, *Le droit des médicaments au Canada et autres produits de santé*, 2d ed. (Cowansville, QC: Edition Yvon Blais, 2010) at 118-21.
55. Health Canada, Guidance Document, Data Protection under C.08.004.1 of the Food and Drug Regulations, March 2010 at 9-10.
56. David L, “Orphan Drug Exclusivity in Canada” http://www.jptcp.com/jtpcpe42_e46_wong2-r199353

How to cite this article:

Ravi Mistry, Dilip Maheshwari: regulatory exclusivity strategies: further protection for pharmaceuticals in us, Europe and Canada, 6(1): 2300 - 2310. (2015)

All © 2010 are reserved by Journal of Global Trends in Pharmaceutical Sciences.