Protection of Pharmaceutical Test Data: A Policy Proposal[1]

Judit Rius Sanjuan- James Love – Robert Weissman[2]

Introduction

Before a new drug is introduced into the market, evidence of its safety, effectiveness and quality must be provided to the national drug regulatory authorities. This can be done by generating and submitting the pharmaceutical test data obtained from test and clinical trials or, as usually done by the generic industry, by relying on the test data submitted by others. There are economic, practical and ethical reasons why second/generic entrants into the pharmaceutical market should not attempt to reproduce the test data. The tests may take several years to complete and delay the entry of cheaper generics into the market; it will also generally be unethical to replicate tests on human subjects for products that have already demonstrated efficacy.

The tests, particularly those involving human clinical trials, are relatively expensive and often require significant investments. Many countries provide legal protection for the test data, which is separate from the rights given to patented inventions.

Before 1984 in the United States, and before 1987 in the European Union, pharmaceutical test data was protected as a **trade secret**, and unfair competition law protections against competition based on dishonest practices. There was no legal prohibition against relying upon published data to establish the safety and efficacy of drugs, and there were even some limited situations where companies were effectively permitted to rely upon unpublished "secret" data that had been submitted to regulators.

Under current regulations, the United States and the European Union grant a period of exclusive rights for the pharmaceutical test data that "originators" (the company that developed the product) generate and submit to national drug regulatory authorities. These regulations prevent generic drug manufacturers and national regulatory authorities from *relying upon* an originator's test data to approve generic applications during a pre-determined period of time. If the generic entrant cannot obtain a "right of reference" (permission to use the test data) from the company that first marketed the product, they

[2] This work was requested by the "International Seminar on Development and Vulnerability: Outlooks for Resuming Development in Southern Countries" organized by the Institute of Economics (IE) at the Federal University of Rio de Janeiro (UFRJ), September 2006 in Rio de Janeiro. This paper is a modified version of two previous CPTech proposals: "US and EU Protection of Pharmaceutical Test Data" (CPTech Discussion Paper No. 1, 2006) available online at http://www.cptech.org/publications/CPTechDPNo1TestData.pdf and "A cost sharing model to protect investments in pharmaceutical test data" (CPTech Policy Brief No. 1, 2006) available online at http://www.cptech.org/publications/policybrief-no1-cost-sharing.pdf

would have to re-conduct the tests, including the human use clinical trials, or wait until the data exclusivity period expires in order to obtain marketing approval. The U.S./E.U. system, sometimes referred as "*marketing exclusivity*" or "*data exclusivity*"[3] is clearly a generic delaying-approval mechanism.

The issue of exclusive rights to rely upon data has become especially relevant since the United States and the European Union, influenced by their brand-name pharmaceutical industries, are urging countries to recognize this practice in a variety of trade negotiations and forums.[4] Although the U.S. system of exclusive rights in data was adopted as part of a larger reform of the drug registration process that, on balance, promoted generic competition, the U.S. and European demands are intended purely to delay generic entry.

However, the granting of the exclusive right to rely upon test data is not required and goes considerably beyond the minimum obligations under the WTO Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS Agreement). The relevant provision in the TRIPS Agreement is Article 39.3.

> **TRIPS** - Section 7: Protection of Undisclosed Information[5]
> **Article 39.3**: "Members, when requiring, as a condition of approving the marketing of pharmaceutical or of agricultural chemical products which utilize new chemical entities, the submission of undisclosed test or other data, the origination of which involves a considerable effort, shall protect such data against unfair commercial use. In addition, Members shall protect such data against disclosure, except where necessary to protect the public, or unless steps are taken to ensure that the data are protected against unfair commercial use."

Article 39.3 by itself is not clear regarding the nature of protection the TRIPS Agreement requires. Under article 39.3, a WTO Member' obligation is limited to the protection from "unfair commercial use" of "undisclosed" data, the origination of which involves a "considerable effort" and that is "used" to register "new chemical entities". Whatever the

[3] The terms "marketing exclusivity," "market exclusivity," "new drug product exclusivity," "Hatch-Waxman exclusivity," "sui generic protection," "data exclusivity," and "data protection" are all found in the U.S. and E.U. legal literature. The term "marketing exclusivity" is used more often in the U.S. regulatory system, and both the terms "data protection" and "data exclusivity" are used in the E.U. system. According to one expert (Interview with Ann Witt, U.S. House of Representative Government Reform Committee, Minority Staff, November 2006): "*Hatch-Waxman never mentions the concept of "data" exclusivity. The law prohibits the marketing of certain generic drugs during a specified period, but does not expressly tie that exclusivity to the data submitted in the application. For example, a new drug that was approved solely on the basis of publicly available data could be entitled to 5-years of exclusivity under Hatch-Waxman and the data supporting the application would remain public. The only requirement for the exclusivity is that the drug contain a never-before-approved active moiety. There is no requirement that the data belong to the applicant. It seems preferable to call Hatch-Waxman exclusivity "marketing exclusivity." Calling it "data exclusivity" could make it harder to argue that FDA could release or use the data in the applications for public purposes*".

[4] In addition to various bilateral and regional trade agreements negotiated by the U.S. or the E.U., and the continuing negotiations over WTO accession, the U.S. makes this issue a leading focus of its Special 301 Report, which is a unilateral listing of countries that do not provide "adequate" intellectual property protection.

[5] Emphasis added.

TRIPS Agreement mandates, it certainly does not require Member States to provide exclusive rights to the originator of the test data.

Experts who have examined this issue and the negotiating history of article 39.3 have concluded that a country can satisfy its TRIPS obligations by simply protecting regulatory data from disclosure or "misappropriation"[6]. Nothing in the TRIPS prevents a WTO member from allowing generic competitors to rely upon public information, evidence of foreign drug registrations, or non-disclosed data from another company (the so-called Non-disclosure model).

This paper first explains the U.S. and European Union models of data exclusivity in some detail. These accounts of the U.S. and EU systems highlight their relatively recent adoption, and in the U.S. case, how they were adopted in the context of other reforms designed to speed up generic entry. Then, recognizing that several countries are facing U.S. and E.U. pressures to implement a TRIPS-plus model and to reject the minimum non-disclosure approach, we briefly outline a series of measures that will lessen the harm from grants of exclusive rights in test data. In the subsequent section of the paper, and again in recognition of pressure on countries to provide data protection beyond the nondisclosure approach, we present a particular approach to implementing TRIPS Article 39.3[7]. Similar to a system used by the United States for agricultural pesticide test data, we advocate a cost-sharing model that would provide a period of protection to data originators, but allow generic companies during this period to rely upon originators' test data if they make reasonable contributions toward the cost of the investments. The model presented in this paper would exceed the minimum requirements of the TRIPS Agreement. It is a compromise between the very modest obligations of the TRIPS and the very high levels of protection given to data in the United States and Europe,[8] and

[6] For example, Carlos Correa: "Protection of Data Submitted for the Registration of Pharmaceuticals: Implementing the Standards of the Trips Agreement". (2002, South Centre). Available at: http://www.southcentre.org/publications/protection/toc.htm

[7] CPTech began working on problems relating the data exclusivity in 1991, in connection with the registration of Taxol, an unpatented cancer drug, and in a number of cases has advocated consideration of compensatory liability or mandatory compulsory licensing of rights in test data, including, for example, October 21, 1997 US Senate hearing (Ibid), and as an option for the CAFTA-US Free Trade Agreement in 2004 (http://www.cptech.org/ip/health/trade/cafta/joyspencercafta.html).

[8] Alternative models to the "EU/US exclusivity regime" have been presented (at least) by: J.R. Reichman: Undisclosed Clinical Trial Data Under the TRIPS Agreement and Its Progeny: A Broader Perspective, (UNCTAD-ICTSD Dialogue on Moving the Pro-Development IP Agenda Forward: Preserving Public Goods in Health, Education and Learning, 2004). Available online at: http://www.iprsonline.org/unctadictsd/bellagio/docs/Reichman_Bellagio4.pdf; R. Weissman: Data Protection: Options for Implementation (Included in the book: Negotiating Health: Intellectual Property and Access to Medicines, Pedro Roffe, Geoff Tansey, David Vivas-Eugui, Earthscan Publications Ltd. 2006); A.X. Fellmeth: Secrecy, Monopoly, And Access To Pharmaceuticals In International Trade Law: Protection Of Marketing Approval Data Under The Trips Agreement (45 Harvard International Law Journal 443, 2004); and R. Dinca: The "Bermuda Triangle" of Pharmaceutical Law: Is Data Protection a Lost Ship? (8(4) Journal of World IP 517, 2005). Earlier proposals for capping exclusivity when sales reach a certain level, and providing for compulsory licensing of the data were presented in an October 21, 1997 US Senate hearing, "Health Registration Data Exclusivity, Biomedical Research, and Restrictions on the Introduction of Generic Drugs," statement of James P. Love, Consumer Project on Technology, before the Subcommittee on Labor, Health and Human Services and Education and Related Agencies, Committee on Appropriations, U.S. Senate. Available online at: http://www.cptech.org/pharm/senhregd.html

explicitly offered as a strategy to offset the heavy political pressure applied on developing countries by the United States and EU to adopt systems of data exclusivity. After presenting the proposal, we briefly outline its advantages and address potential criticisms.

UNITED STATES[9]

Before 1984, U.S. legal protection for an applicant's unpublished safety and efficacy data was basically provided by a limited trade secret protection regime[10].

Prior to 1962, new drugs in the U.S. were approved by proving safety only, and for generic competitors the existence of a drug on the market was usually sufficient for that purpose. In 1962, the U.S. Federal Food, Drug, and Cosmetic Act was amended to require pharmaceutical manufacturers to demonstrate that their new products were both safe and effective.

The 1962 amendments did not contain any provision for a separate approval process for drugs that were identical to drugs previously approved. Generic manufacturers were thus compelled to file a New Drug Application (NDA) and to submit evidence proving that the generic drug was safe and effective, even if their product was chemically identical to one previously approved.

However, there were important exceptions to the 1962 safety and efficacy requirements. The generic applicants were allowed to prove only bioequivalence -- that their product is pharmaceutically the same and works the same in the body as the originator product -- in two situations:

a) **Pre-1962 drugs.** When relying on a drug that had been approved before October 1962, the generic manufacturer had only to demonstrate bioequivalence with the product already on the market, while when relying on a drug approved after 1962, the generic manufacturer also had to demonstrate safety and efficacy.

b) **Special regime for Antibiotics.** In the case of antibiotics, the distinction between pre- and post-1962 drugs did not exist. An abbreviated process for approving generic antibiotics, which only required tests to show bioequivalence,

[9] For some background reading: A. Engelberg: Special Patent Provisions for pharmaceuticals: have they outlived their usefulness? 39 J.L. & Tech. 389 (1999); A. Engelberg: Data Exclusivity under Article 39.3 of TRIPS – Does current US law comply? Working Paper, October 22 (2001); G. Mossinghoff: Overview of the Hatch-Waxman Act and its impacts on the Drug Development. Food and Drug Law Journal, Vol. 54; How Increased Competition from Generic Drugs has affected process and returns in the Pharmaceutical Industry. CBO (1998); M.P. Pugatch: Intellectual Property and pharmaceutical data exclusivity in the context of innovation and market access. ICTSD-UNCTAD Dialogue on Ensuring Policy Options for Affordable Access to Essential Medicines Bellagio (2004); R. Strongin: Hatch-Waxman, Generics, and Patents: Balancing Prescription Drug Innovation, Competition, and Affordability. NHPF Background Paper (2002); and V. Junod: Drug marketing exclusivity under United States and European Union law. 59 Food & Drug L.J. 479 (2004).

[10] FDA regulations 21 CFR § 314.14 (f), codified in 1984 in the Section 21 U.S.C. § 355 (l).

applied to all antibiotic drugs approved under section 507 of the Federal Food, Drug, and Cosmetic Act.

Drugs could also be approved based on a **"paper" new drug application (NDA)**, which allows the applicant to rely on published scientific literature demonstrating the safety and efficacy of the drug and not on the result of the original testing by the NDA applicant. However, these sorts of studies were not available for all drugs. Moreover, nothing in the FDA regulations prevented the Agency from requesting additional studies. According to one expert[11], getting a paper NDA approved was an uncertain and expensive undertaking.

In 1984 a major pharmaceutical legislative reform took the form of the **Drug Price Competition and Patent Term Restoration Act**, also known as the Hatch-Waxman Act[12].

The 1984 Hatch-Waxman Act effectively extended the Abbreviated New Drug Application (ANDA) processes that existed for antibiotics (and under certain conditions to pre-1962 drugs) to all generic drugs, allowing generic manufacturers to gain FDA marketing approval by relying on safety and efficacy data from original NDA, so long as the generic drug was bioequivalent with the originator's drug[13]. The 1984 amendments also introduced a new kind of application: the 505(b)(2) applications[14].

Possible second applicants' entrance into the U.S. Market: Since 1984, there have been two possible ways a "second applicant" company can file for drug approval: with an ANDA or a 505(b)(2) Application. Both ANDAs and 505(b)(2) applications imply reliance, in full or in part, on the test data prepared by a third party, usually the sponsor of the reference drug or originator.

The end of Paper NDA Applications: The introduction of ANDA and 505(b)(2) applications; which allow reliance upon unpublished data, eliminated the need

[11] Interview with Alfred Engelberg (April 2006)
[12] Pub. L. No. 98-417 (98th Congress, 1984).
[13] Abbreviated new drug applications (ANDA) are regulated in section 21 U.S.C. § 355(j). These are the most common form of generic applications. Applications must contain information to show that the proposed product is identical or almost identical in active ingredient, dosage form, strength, route of administration, labeling, quality, performance characteristics and intended use, among other things, to a previously approved application (the originator or reference listed drug). ANDAs do not contain clinical studies but are required to contain information establishing bioequivalence to the originator. In general, the bioequivalence determination allows the ANDA to rely on the agency's finding of safety and efficacy for the originator.
[14] 505(b)(2) Applications are regulated in section 21 U.S.C. § 355(b)(2). These applications are for drugs that are only somewhat similar to another drug (e.g. the same composition but a new indication), and for which one or more of the investigations relied upon by the applicant for approval "were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted". When approving a 505(b)(2) application, the FDA can rely on data not developed by the applicant such as published literature or the agency's finding of safety and effectiveness of a previously approved drug. For more information: "Guidance for Industry Applications Covered by Section 505(b)(2)" (1999). Available at http://www.fda.gov/cder/guidance/2853dft.pdf

for FDA's paper NDA applications, which permitted the approval of duplicate drugs through reliance upon published data.

The 1984 Hatch-Waxman Act also introduced several non-patent-marketing exclusivity regulations (see box below). In this paper, we are going to focus on the so-called **"New drug product exclusivity".** The inclusion of marketing exclusivity regulations has been attributed to a political bargain that took place in 1984 when the United States allowed second applicants to register products when they establish bioequivalence with a product that had already received marketing approval, relying on that originators' test data demonstrating the safety and efficacy (the ANDA and 505 (b)(2) applications) and the "Bolar" exception to patent rights[15]. Both measures were introduced to promote competition from the generic industry.

The current U.S. marketing exclusivity regulations are quite complex and co-exist with a number of other non-patent provisions that extend marketing exclusivities, including:
- Orphan drug exclusivity: 7 years
- Pediatric drug exclusivity[16]
- Generic drug exclusivity[17]
- Drugs approved between 1982 and 1984
- Medical devices exclusivity

As well as special provisions relating to patent protection and extensions of patent term.

The New Drug Product Exclusivity is regulated in Section 355 of the Federal Food, Drug and Cosmetic Act. National regulatory authorities are prevented from relying on the originator's test data to approve subsequent applications during a pre-determined period of time. There are two categories of product exclusivity:

a) A **5-year period** of exclusive rights from the date of FDA approval is granted to new drug products containing new chemical entities.

The main condition for receiving this 5-year exclusive right is that the approved new drug application contains a new active ingredient -- that is, a New Chemical Entity (NCE)[18] or

[15] Certain practices related to obtaining FDA approval that would otherwise constitute patent infringement are exempted from infringement liability under the patent laws. Most importantly, the U.S. "Bolar" exception is in Section 35 USC 271(e)(1), which reads in part: "It shall not be an act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented invention . . . solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products".

[16] Pediatric exclusivity is six months and can be added to other exclusivities or patent protections. It is the only exclusivity that runs from the end of other exclusivity protection (New Drug Product and Orphan Drug) or patent protection (and thus may function as a de facto patent extension).

[17] To encourage generic producers to seek early entry of their products onto the market (including by challenging the validity of patents with a paragraph IV certification), the first generic company that successfully applies for approval of a generic version of an originator product may have a 180-day period of exclusivity. 21 USC 355 (j)(5)(B)(iv)(I)

new active moiety[19] -- not previously approved by the FDA alone or in combination with other chemical entities.

> "Relative" novelty: in the U.S., a drug is treated as an NCE if it contains an active moiety that has not been approved by the FDA, although it may not be "universally" novel because such active moiety may already be known or described in scientific or technical literature.

The effect of this exclusivity is that *no* ANDA[20] or 505(b)(2)[21] applications may be submitted during the 5-year exclusivity period.

> Because the FDA takes an average of 18 months to approve a generic application, the five-year marketing exclusivity delays competition by about 6.5 years following the date of the reference drug's approval.

The five-year period may be reduced to **four years** if the second/generic application contains a certification of patent invalidity or non-infringement (Paragraph IV Certification[22]).

b) A **3-year period** of marketing exclusivity from the date of the FDA approval is granted to new uses/indications of drug products containing an active moiety that has been previously approved, when the application contains reports of new clinical investigations conducted or sponsored by the applicant that were essential to the approval of the application or the supplement.

The main conditions for grant of this three-year period of exclusivity are that a new use/ indication is discovered and that the pharmaceutical company must have conducted or

[18] The FDA interprets the term "New Chemical Entity" as a drug that contains no active moiety that has been approved by FDA in any other application submitted under section 505(b) of the Act.
[19] The FDA interprets the term "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 noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance.
[20] 21 U.S.C. § 355(j)(5)(F)(ii)
[21] 21 U.S.C. § 355(c)(3)(E)(ii)
[22] Section 21 U.S.C. § 355(c)(3)(E)(ii) stays that: "….except that such an application may be submitted under subsection (b) after the expiration of four years from the date of the approval of the subsection (b) application if it contains a certification of patent invalidity or non-infringement described in clause (iv) of subsection (b)(2)(A)…." U.S. Law provide that second applicants/generic have four certification options, Paragraph IV certification indicates that the generic intends to market the drug as soon as the FDA approves the application because the patent is invalid or will not be infringed by the generic drug for which the applicant seeks approval. For more information see CPTech Discussion Paper N.2 on Patent-Registration linkage (2006), available online at: http://www.cptech.org/publications/CPTechDPNo2Linkage.pdf

sponsored[23] new clinical trials/investigations[24] (other than bioavailability studies) which were essential for the approval of the new drug application or supplement.

Contrary to the five-year exclusivity, this three-year exclusivity allows the FDA to receive and review ANDA or 505(b)(2) applications before market exclusivity has expired. The FDA can even grant tentative approval, but the approval becomes effective only after the three-year period has elapsed. The second applicant can thus market its product immediately following expiry of the three-year exclusivity.

How does this system work in practice?

1. The Center for Drug Evaluation and Research (CDER) makes exclusivity determinations on all the relevant new drug applications, with or without a request from the new drug applicant.

2. The generic companies use the FDA publication "Approved Drug Products with Therapeutic Equivalence Evaluations", commonly known as the **Orange Book**, to find information on drugs that have received New Drug Product Exclusivity[25].

> **In a few words:** Marketing exclusivity in the U.S. provides the originator of a drug with a limited protection precluding for a prescribed period of time the approval of registration applications that rely on the originator's test data.
>
> Five years exclusivity is provided for drugs with new chemical entities; and 3 years exclusivity is provided for new uses/indications in already approved drug products.

[23] The FDA interprets "conducted or sponsored" as involving clinical trials where, before or during the investigation, the applicant was named in Form FDA 1571 as the sponsor of the investigational new drug application under which the investigation was conducted, or the applicant or the applicant's predecessor in interest, provided substantial support for the investigation. An applicant who has purchased exclusive rights to a study should also be able to obtain new drug product exclusivity. Applicants cannot qualify for exclusivity by simply collecting and submitting to FDA information from the literature or buying the results of tests already done and submitting them to FDA without obtaining exclusive rights for those tests. The applicant is not required to conduct the complete study to obtain exclusivity; it is enough when the applicant has provided 50 percent of the funding or by purchasing exclusive rights to the study.

[24] The FDA interprets "new clinical investigation" as an investigation in humans, the results of which (1) have not been relied upon by the FDA to demonstrate substantial evidence of effectiveness of a previously approved drug product for any indication or of safety in a new patient population and (2) do not duplicate the results of another investigation relied upon by the FDA to demonstrate a previously approved drug's effectiveness or safety in a new patient population. A clinical investigation that provides a "new" basis for approval of an application can qualify for exclusivity. In this context, "new" is intended to convey a lack of prior use of a clinical investigation rather than any temporal requirement.

[25] The electronic version of the Approved Drug Products with Therapeutic Equivalence Evaluations/ Orange Book is available at http://www.fda.gov/cder/ob/default.htm

Special Regime: Antibiotics and U.S. Marketing Exclusivity

The Title I of the 1984 Hatch-Waxman Law that introduced marketing exclusivity in the U.S did not cover antibiotics because an abbreviated process for approving generic antibiotics, which only required tests to show bio-equivalence, already applied to all antibiotic drugs approved under old section 507 of the Federal Food, Drug, and Cosmetic Act[26].

However, the Food and Drug Administration Modernization Act (FDAMA) of 1997 made antibiotic drugs submitted after the FDAMA effective date (November 20, 1997), eligible for Hatch-Waxman exclusivities. The 1997 FDAMA repealed the old section 507 and required companies that want to market new generic antibiotics to file the same kind of application (section 505) as all other generic drugs.

An application for a drug that contains an antibiotic, in which the antibiotic was the subject of any application for marketing received before November 21, 1997 (an old antibiotic), is not eligible to receive marketing exclusivity (and is not subject to certain Orange Book patent listing and notification requirements) applicable to drugs approved under section 505. Section 125 of FDAMA exempts from the marketing exclusivity provisions, marketing applications for drugs that contain old antibiotics, by providing that "[drugs that were approved and marketed under former Section 507 of the FD&C Act, as well as those that were the subject of applications that may have been withdrawn, not filed, or refused approval under Section 507 of the FD&C Act are excluded from the patent listing and exclusivity provisions."

According to one expert[27] because of the broad definition of antibiotic in section 125 of FDAMA, FDA interprets[28] the exclusion from exclusivity for old antibiotics to be somewhat broader than just the antibiotic drug products actually approved under section 507. FDA interprets section 125 to exclude not only specific drugs approved under 507 but also any drugs that include the "active moiety" in a drug approved under 507. This means that minor chemical variations (e.g., new salts and esters or other non-covalent derivatives) of old antibiotics are also excluded from eligibility for exclusivity.

For more information, see FDA Guidance for Industry and Reviewers Repeal of Section 507 of the Federal Food, Drug and Cosmetic Act[29].

Recommended reading: FDA's Frequently Asked Questions for New Drug Product Exclusivity. Available online at: http://www.fda.gov/cder/about/smallbiz/exclusivity.htm

[26] Source: FDA FAQ on patents and exclusivity, available at: http://www.fda.gov/cder/ob/faqs.htm
[27] Interview with Ann Witt, U.S. House of Representative Government Reform Committee, Minority Staff (November 2006)
[28] A useful description of FDA's understanding of the situation is found in the preamble to its proposed (not finalized) rule to implement section 125 of FDAMA, available at: http://www.fda.gov/cder/fdama/fedreg/01242000.pdf
[29] Available online at: http://www.fda.gov/cder/guidance/2468fnl.pdf

EUROPEAN UNION[30]

Before 1987, the European Union data protection regime was basically a trade secret regime and varied considerably from country to country.

Europe harmonized its medicinal products[31] marketing authorizations in 1965 with the Council Directive 65/65/EEC[32]. The 1965 Directive established that a pharmaceutical company applying for marketing approval should present results of test and clinical trials demonstrating a product's safety and efficacy.

The trade secret protection of test data was not addressed in the 1965 Directive. The Directive did not consider use of such data by drug regulatory authorities to approve another drug. However, in 1984 the European Commission recognized the concept of "indirect use of such data" when it noted that "certain national authorities tended not to be too demanding in their assessment of the adequacy of published references, even where data on safety were incomplete," suggesting there was recognition that some regulators allowed generic competitors to effectively rely upon data that was controlled by the originator.

There were also exceptions. The 1965 Directive recognized one application procedure that did not require applicants to present the full efficacy and safety data testing – the "abridged procedure"[33] for "published literature exemption" where adequate data existed in the public domain (similar to the U.S. Paper NDA application).

The European Union introduced data exclusivity for the first time in 1987 with the **87/21/EEC Directive**[34], which amended the 65/65/EEC Directive.

[30] For background reading, see: I. Dodds-Smith: Data Protection and abridged applications for marketing authorizations in the pharmaceutical industry (from the book: Goldberg, Richard and Lonbay, Julian, (Eds.): Pharmaceutical Medicine, biotechnology and European Law, Cambridge University Press, 2000); M.P. Pugatch: Intellectual Property and pharmaceutical data exclusivity in the context of innovation and market access. ICTSD-UNCTAD Dialogue on Ensuring Policy Options for Affordable Access to Essential Medicines Bellagio (2004); and V. Junod: Drug marketing exclusivity under United States and European Union law. 59 Food & Drug L.J. 479 (2004).

[31] In E.U. terminology, "pharmaceutical products" are refereed to as "medicinal products".

[32] Council Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by Law, Regulation or Administrative Action relating to proprietary medicinal products. Available at: http://europa.eu.int/smartapi/cgi/sga_doc?smartapi!celexapi!prod!CELEXnumdoc&lg=EN&numdoc=365L0065&model=guichett

[33] In Europe, subject to certain conditions, applicants submitting "abridged applications" are not required to provide the results of pharmacological and toxicological tests or the results of clinical trials and can rely on the data presented by a pioneer application. The abridged applicant remains obliged to provide the other particulars and documents listed in Article 8.3 of Directive 2001/83, including physico-chemical, biological or microbiological tests.

[34] Council Directive 87/21/ECC of 22 December 1986, amending Council Directive 65/65/EEC on the approximation of provisions laid down by law, regulations or administrative action relating to proprietary medicinal products. Available at: http://europa.eu.int/smartapi/cgi/sga_doc?smartapi!celexapi!prod!CELEXnumdoc&lg=EN&numdoc=387L0021&model=guichett

The 1987 Directive, as well as several others, was consolidated in 2001 in a single **Community Code**, the Directive 2001/83/EC[35].

The 1987 Directive also introduced a new harmonized procedure for abridged applications for "essentially similar" products, the classic generic applications[36]. Since 1987, European second/generic applicants for medicinal products that show that their product is "essentially similar" to a product already authorized can rely[37] on the test data submitted by the first applicant and present abridged applications in the specific E.U. countries where the relevant period of data exclusivity has expired and the product is marketed.

In a 1998 case, the European Court of Justice (ECJ) defined an essentially similar medicinal product as one: "where it satisfies the criteria of having the same qualitative and quantitative composition in terms of active principles, of having the same pharmaceutical form and of being bioequivalent, unless it is apparent in the light of scientific knowledge that it differs significantly from the original product as regards safety or efficacy" [38].

Possible second applicants' entrance into the E.U. Market:

The essentially similar abridged procedure is the typical application for generic products in the European Union.

If, however, the generic medicinal product is intended for a different use, or for different dosage forms or different forms of administration, then the results of appropriate pharmacological and toxicological tests and/or appropriate clinical trials, must be provided. This proviso is known as the "hybrid application"[39].

As is the case in the United States, a second applicant with a right of reference/use from the pioneer company is entitled to rely on the latter's data before the data exclusivity period has expired[40].

Second applicants may also seek marketing approval via the "Published Literature Exemption", where the second applicant presents references to

[35] 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. Available at: http://pharmacos.eudra.org/F2/eudralex/vol-1/DIR_2001_83/DIR_2001_83_EN.pdf. In 2003, the 2001/83/EC Directive, and more specifically its Annex I, was modified by the Commission Directive 2003/63/EC of 25 June 2003, 2003 O.J. (L 159) 46. The text is available at: http://pharmacos.eudra.org/F2/review/doc/2003_June/direct_comm_2003_63_es%20.pdf

[36] Article 10.1(a) of Directive 2001/83 (formerly Article 4.8(a) of Directive 65/65, as amended by Directive 87/21) provides for an abridged authorization procedure.

[37] The E.U. interprets the notion of "reliance" in much the same way as the United States; indeed, the notion refers to reliance by the drug agency, and not to direct access and use of the data by the second applicant.

[38] C-368/96 Generics (UK) and Others [1998] ECR I-1967

[39] Regulated in second subparagraph of Article 10.1(a)(iii) of the Directive 2001/83/EC

[40] These types of applications are referred as "informed consent" abridged applications. Article 10.1(a)(i). This had always been possible although before 1987 it was not expressly mentioned.

published scientific literature demonstrating that the product has "well established medicinal uses", is also a possibility[41]. After the Scotia[42] and Taxol[43] litigations, however, the exemption was amended and E.U. legislation now mandates[44] a minimum period of a decade to demonstrate a well-established use of a constituent of a medicinal product. The period begins with the first systematic and documented use of that substance as a medicinal product in the E.U.

At the time of introduction in 1987, the data exclusivity regime in Europe was justified to afford some degree of protection to research-based pharmaceutical companies in European Member States that did not confer patents to pharmaceuticals[45] and that were faced with the new process for approval of generic competitors.

In July 2001, the E.U. launched an initiative to revise key aspects of its pharmaceutical legislation, data exclusivity being one of the key topics. The result was the **2004/27/EC Directive**[46] that amended Directive 2001/83/EC. Member States had until October 30, 2005 to implement the new revised Directive. However, the new data protection harmonized periods will benefit only drugs submitted for authorization after the implementation date. Originator drugs approved before that date remain subject to the 2001 system. Therefore, most abridged/generic applications to be filed in the next ten years will be based on the old 2001 system.

The EU data exclusivity system is further complicated by the fact that different forms of protection are provided depending on how an originator product was granted marketing approval. These different methods are summarized in the accompanying box below.

Possible applicants' entrance into the E.U. market:

A pharmaceutical company wanting to get marketing approval for a medicinal product in the European Union has several options:

a) National procedures to approve medicinal products that will be sold only on the domestic market.

[41] Article 10.1(a)(ii) of Directive 2001/83 (formerly Article 4.8(a)(ii) of Directive 65/65, as amended by Directive 87/21) regulated the published literature exemption.
[42] Case C-440/93 R v. 1. Licensing Authority of the Department of Health and 2. Norgine Ltd, ex parte Scotia Pharmaceuticals LTD (1995) ECT I-2851
[43] Bristol-Myers Squibb BV v. Het College ter Beoordeling Van Geneesmiddelen (Medicines Evaluation Board) and Yew Tree Pharmaceuticals BV. Ultrecht District Court, 2000
[44] Article 10a of the Directive 2001/83/EC, as amended
[45] For example, until 1992, Spain and Portugal did not grant product patents to medicinal products. Product patents for medicinal products are now available in all 25 Member States.
[46] Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use. Available at: http://pharmacos.eudra.org/F2/review/doc/final_publ/Dir_2004_27_20040430_EN.pdf

b) Mutual recognition procedure (decentralized) to approve medicinal products that will be marketed in several Member States.

c) London-based European Medicines Agency (EMEA) Centralized procedure[47] to approve "eligible" medicinal products[48]. Medicinal products obtain a single marketing authorization, in the form of a Commission decision, valid in all Member States.

The data exclusivity regimes in Europe:

A) For Drugs Placed on the Market Before 2005: Directive 2001/83/EC

The E.U. period of data protection starts running with the first marketing authorization of the medicinal product in any Member State of the European Union. There are four different lengths of exclusivity:

- a ten-year mandatory period: for high-tech medicinal products that are approved by the EMEA through the centralized procedure.

- a six-year minimum period[49]: for all other drugs, drugs approved through either the mutual recognition procedure or the national procedure of an individual Member State.

- a six-year minimum period capped by the patent duration[50]: Member States that apply the six-year minimum period may choose to cap this period at the instant the patent protecting the drug expires, so data exclusivity will not extend beyond the period of the patent protection.

- a ten-year optional period[51]: based on a finding that it is "necessary in the interest of public health". Member States may decide to extend the six-year period of protection up to a ten-year ceiling to all eligible pharmaceuticals marketed in their territory; they may not discriminate on the basis of the country of origin.

[47] European Commission, Notice to Applicants, Centralized Procedure, in Vol. 2A, PROCEDURES FOR MARKETING AUTHORISATION, ch. 4, at 2-3 (Dec. 2002). Available at:http://pharmacos.eudra.org/F2/eudralex/vol-2/A/v2a_ chap2%20_r3_2004-02.pdf

[48] Presently, only so-called "high-tech" products are eligible for approval through this centralized procedure. These are drugs derived from biotechnology (e.g., recombinant DNA), and products with a significant innovation or therapeutic advance, including new active substances, new therapeutic indications, new delivery systems, and new manufacturing methods.

[49] Austria, Denmark, Finland, Greece, Ireland, Portugal, Spain, Norway and Iceland and the 10 new 2004 Member States (Cyprus, the Czech Republic, Estonia, Hungary, Latvia, Lithuania, Malta, Poland, Slovakia, and Slovenia) have opted for this solution.

[50] Greece, Spain, and Portugal have opted for this solution.

[51] Belgium, Germany, France, Italy, The Netherlands, Sweden, the United Kingdom, and Luxembourg have opted for this solution.

Contrary to U.S. law, current E.U. data exclusivity does not grant additional periods of protection for subsequent improvements brought to a drug, for example new therapeutic indications, dosage forms, doses and dosage schedules [52] or formulations[53].

The current European regime has some ambiguities. To be awarded a period of data protection, the first applicant must have obtained marketing approval for a new medicinal product. The Directive does not specify whether the product has to be an entirely new chemical entity.

Furthermore, the European legislation does not make it clear whether second entrants are authorized to submit their application for review before the data exclusivity has expired, or if they have to wait for expiry before filing their application. The European Generic Medicines Association (EGA) argues that, in practice, the rule is the latter. According to the EGA, "the effective period of marketing exclusivity gained by the originator company is the period of data exclusivity (6 or 10 years) plus the time it takes to register and market the generic medicine – a further 1 to 3 years" [54].

> **In a few words:** The E.U. data exclusivity regime guarantees market protection for originator medicines for either 6 or 10 years depending on the Member State national legislation. A 10-year period is granted to an originator gaining marketing approval through the EMEA Centralised Procedure.

B) For Drugs Placed on the Market In 2005 or Later: Directive 2001/83/EC (as amended by Directive 2004/27/EC)

The new 2001/83/EC Directive[55] introduces **a harmonized "8+2+1" formula** for new drugs approved either through the centralized procedure or the mutual recognition procedure.

The new E.U. pharmaceutical legislation establishes an **eight-year Data Exclusivity**, starting with the initial approval of the "European reference medicinal product"[56] + **two-year Market Exclusivity**. The second/generic applicant can not submit its request for a marketing authorization referencing the originator data during 8 years starting from the initial approval of the reference medicinal product; after this 8 year period expires the

[52] C-368/96 R v. The Licensing Authority established by the Medicines Act 1968 (acting by the Medicines Control Agency), ex parte Generics (UK) Ltd; R v. Same, ex parte Wellcome Foundation Ltd; R v. Same, ex parte Glaxo Operations UK Ltd and Others (E.R. Squibb & Sons Ltd, Generics (UK) Ltd, intervening) [1999] ECR I-7967 ("The Generic Case")

[53] C-94/98 R v MCA ex parte RPR and R v MCA ex parte RPR, Trinity Pharmaceuticals and Norton Healthcare Intervening ("The RPR Zimovane Case")

[54] Available at: http://www.egagenerics.com/gen-dataex.htm

[55] A not official consolidate version is available at: http://pharmacos.eudra.org/F2/eudralex/vol-1/CONSOL_2004/Human%20Code.pdf

[56] The 2004 Directive creates the "European reference product". Now, a generic applicant can apply for a marketing authorization in any Member State and rely on the dossier already submitted from the European Reference Product in another Member State. The other Member State will be obliged to supply the documentation requested.

generic can submit an application and get preliminary approval but the authorization is not made effective and the product can not be placed in to the market until the following 2 year period expires[57].

This effective 10-year market exclusivity can be extended by an **additional one year maximum** if, during the first eight years of those ten years, the data originator obtains an authorization for one or more new therapeutic indications which, during the scientific evaluation prior to their authorization, are held to bring a significant clinical benefit in comparison with existing therapies.

The 2004 legislation also provides that new strengths, pharmaceutical forms, routes of administration, and presentations, as well as any extensions or variations, are to be considered as belonging to the same "global authorization" for purposes of the abridged application rules[58] and therefore there is no data protection for these changes[59].

Implementation: The 8+2+1 formula will apply to all Member States, unless certain new Member States are awarded derogations, which they can request following publication of the new law.

In a few words: the New EU Pharmaceutical Legislation adopted in 2004 has created a harmonized E.U. eight-year data exclusivity provision with an additional two-year market exclusivity provision. This effective 10-year market exclusivity can be extended by an additional one year maximum if the originator obtains an authorization for other new therapeutic indications with a significant clinical benefit.

Other Data Exclusivity Regimes:

The European revised legislation also provides that:

a) "Well-established" products are entitled to receive a one-year data protection period if they are granted approval for a new therapeutic indication. Contrary to new products, the corresponding request (for approval of this new indication) can be made at any time. The applicant must establish that "significant preclinical or clinical studies were carried out" to demonstrate the safety and/or efficacy of this new indication. This latter provision is non-cumulative, it covers only the use of the new indication, and can only be used once. It is not clear what constitutes "a significant clinical benefit".

[57] See chart and summary from the European Generic Medicines Association. Available at: http://www.egagenerics.com/gen-dataex.htm

[58] Article 6.1 of the Directive 2001/83/EC, as amended.

[59] This provision is in line with some recent ECJ decisions which held that a generic application could rely on data relating to a reference product even though the generic product was not essentially similar to the reference product (for example, due to a difference in their pharmaceutical forms. C-106/01, Novartis Pharmaceuticals (ECJ Apr. 29, 2004) and Eli & Lilly & Co. (ECJ Dec. 9, 2004).

b) The 2004 Directive also recognizes one-year data exclusivity for products switching from "prescription-only" (Rx) to "over the counter" (OTC) status, on the basis of significant pre-clinical tests or clinical trials.

"Essentially Similar" v. "Generic"

Before the 2004 Directive, the typical generic abridged procedure was available for "essentially similar" products. Since 2004, the abridged procedure is going to be available only for "generics of reference medicinal products".

> A "generic medicinal product" is defined in article 10.2 as a product which **"has the same qualitative and quantitative composition** in active substances and the **same pharmaceutical form** as the reference medicinal product that is bio-equivalent with the reference medicinal product and has been demonstrated by appropriate bioavailability studies. The **different salts, esters,** ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance should be considered to be the same active substance, unless it differs significantly in properties with regard to safety and/or efficacy. In such cases, additional information providing proof of the safety and/or efficacy…must be supplied by the applicant. The various **immediate-release oral pharmaceutical forms** shall be considered to be one and the same pharmaceutical form. Bioavailability studies need not be required if the applicant can demonstrate that the generic medicinal product meets the relevant criteria as defined in the appropriate detailed guidelines."

The definition of "generic medicinal product" does not seem to include different non-oral pharmaceutical forms, products incorporating a different indication, strength, form or route of administration that used to be considered "essentially similar". Therefore, these products now have to be authorized under the Article 10.3 of the Directive (the "hybrid application") and the results of the appropriate pre-clinical tests or clinical trial must be provided.

"Bio-similar medicinal products": For the first time, the 2004 Directive recognizes that manufacturers of generic bio-pharmaceuticals can follow an abridged procedure[60].

[60] Article 10.4 of the Directive 2001/83/EC, as amended. See also several EMA/ Committee for Medicinal Products for Human Use (CHMP) Guidelines on Similar Biological Medicinal Products. Available at: http://www.emea.eu.int/htms/human/biosimilar/biosimilarfin.htm

COMPARATIVE

	WTO TRIPS	**United States[61]**	**European Union[62] (Post 2004)**
Data protected	Only undisclosed data which involves considerable effort to originate and the submission of which was required	No mention	No mention
Kind of protection	No Unfair Commercial use / disclosure	Granting of exclusive rights No use/disclosure + no reliance permitted	Granting of exclusive rights No use/disclosure + no reliance permitted
New drug protected	Only New Chemical Entity	New Chemical Entities (NEC) + New indications/uses	New Medicinal Product + New indications/uses
Minimum period of protection	No mention	5 years data exclusivity for NEC (non disclosure/reliance) + 3 years market exclusivity for new indications (non disclosure)	8 years data exclusivity (non disclosure/reliance) + 2 years market exclusivity (non disclosure) + 1 year market exclusivity for new indications (non disclosure)

[61] Federal Food, Drug and Cosmetic Act – USC 355
[62] Directive 2001/83/EC, as amended by the 2004/27/EC Directive

OBJECTIONS TO DATA/MARKETING EXCLUSIVITY APPROACH

There are a number of objections to the imposition of a Data Exclusivity/Marketing Exclusivity approach. These include:

- The granting of exclusive rights in test data will delay the entry of generic products into the market, impeding access to affordable medicines.

- It is both unethical and wasteful to ask for duplication of clinical trials. Yet faced with data exclusivity rules, the only way a generic entrant can get on the market during the period of exclusivity without authorization of the originator is to repeat already conducted clinical trials.

- It is a form of double protection, since strong patent rights are justified by the cost of investments in test data. According to this line of thinking, stronger rights in the data should be offset by weaker protections for the patent.

- It is unclear whether the data exclusivity regimes prevent a second entrant/generic from initiating the procedures for the marketing approval "before" the expiry of the exclusivity period. It could undermine the Bolar/Early Working Patent Exception, which seeks to encourage quick access to the post-patent market for generic medicines by exempting from patent liability certain conducts.

- Unless the exclusive rights in the data can be overridden, it can make compulsory licenses of patents or government use orders ineffective.

A real example: European Union Data Exclusivity & Bird Flu Pandemic

An example of how data exclusivity regimes can harm public health is contained in a letter that Martin Terberger of the European Commission[63] sent to the European Generic Medicines Association (EGA). The letter[64] responds to an EGA inquiry on the role that data exclusivity regime could play in case of a compulsory license of the Tamiflu patents[65]. The European Commission confirmed the worst fears of data exclusivity critics by arguing that the regime will delay or prevent European Member States' ability to use compulsory licensing to permit generic substitutes of Tamiflu on the market in case of a Bird Flu pandemic. This situation is startling not only because of the potential severity of a bird flu pandemic, but because concerns surrounding Tamiflu focused less on high prices than on the fact that the

[63] Head of Pharmaceuticals Unit. Enterprise and Industry Directorate-General, European Commission
[64] Letter available at: http://www.cptech.org/ip/health/dataexcl/ec-de-tamiflu.pdf
[65] Tamiflu is the trade name under which Roche is marketing oseltamivir, an antiviral drug that is used in the treatment and prophylaxis of both Influenza virus A and B.

manufacturer, Roche, was unable to provide an adequate supply to meet stockpile needs.

The letter contains the following language: "*the European Pharmaceutical legislation does not foresee any exception to the above mentioned periods of 8 years of data exclusivity and 10 years marketing protection in case of emergency situations or in case a compulsory license has been granted by an EU Member State. This means that a applicant for a marketing authorization in the EU would have to provide the required documentation on pre-clinical tests and clinical trials as required under Article 8(3)(i) of Directive 2001/83/EC, or submit an informed application under Article 10c of Directive 2001/83/EC*" and concludes "*National emergency provisions in a EU Member State may allow the granting of a compulsory patent license which would allow a generic or other company to use the patented product in the Member State in Question. However, the Community pharmaceutical acquis does not currently contain any provision allowing the waiver of the rules on data exclusivity and marketing protection periods described above in the case of a national or an EU-wide emergency*".

There are, moreover, heightened concerns about U.S. and E.U. demands that developing countries adopt data exclusivity regimes:

- There is no obligation in the TRIPS Agreement to grant exclusive rights in test data, and it is inappropriate to ask developing countries for more extensive and higher levels of intellectual property protection for pharmaceuticals than were set out in the TRIPS.

- The export of the U.S. Hatch-Waxman regime to other countries with very different income levels and health conditions has been strongly criticized by one of its proponents, Representative Henry A. Waxman, who has also noted that data exclusivity was included in Hatch-Waxman as part of a deal that, overall, eased generic entrance into the market.[66]

- Delays in generic competition in poorer developing countries will have much more severe effects than the already serious consequences in industrialized nations. To an extent far greater than in industrialized nations with more evolves systems of public and private insurance, in developing countries, the high prices associated with marketing monopolies means that many people simply go without medicines they need.

[66] Statement of Congress Representative Henry A. Waxman at the House Committee on Ways and Means (June 2003). Available at: http://waysandmeans.house.gov/hearings.asp?formmode=printfriendly&id=1107

SAFEGUARDS TO A DATA/MARKETING EXCLUSIVITY REGIME

We believe countries should not include data exclusivity/marketing exclusivity provisions in their national law. The TRIPS Agreement does not require providing any such marketing exclusivities, and they can exact a high public health toll by delaying the introduction of price-lowering generic competition.

However, if countries decide that they must provide some type of protection, for example as a consequence of trade agreements with the United States or the European Union, there are several steps that can be take to reduce the provision's negative effects:

1. Shorten the period of protection: there is no TRIPS obligation to impose five-or ten-year terms of protection[67].

2. Protect only undisclosed data, not data that is already published or publicly available[68].

3. Protect only the test data for which submission was required and relied on by the national authority. Therefore, if the national authority relies upon an approval granted in a foreign country, the obligation of protection should not apply[69].

4. Protect only "New Chemical Entities[70]" (NCEs), not new uses/indications. A restrictive definition of NCE is necessary: molecules that were not previously incorporated within a product or published; excluding second indications, new formulations or dosage forms[71].

5. Adopt a worldwide definition of NCEs: The data exclusivity period should start at the time the originator drug is first approved in anywhere in the world, or, at very least, at the time the originator drug is first approved in a party to the agreement[72].

[67] The TRIPS legislative history had a prior Brussels draft (1990) providing that data exclusivity had to run "for a reasonable time, generally no less than five years". The exclusion of this language from the final version of TRIPS endorses the reading that members are free to determine a period of protection that they consider in accordance with their national interest.

[68] Such a limitation, however, is prohibited by the US/Singapore, US/Morocco, and US/Central America Free Trade Agreements, which require exclusivities for "information" submitted by originators -- without the "undisclosed" qualification.

[69] For example, Canada grants exclusivity only if there is actual reliance, in that the authority has actually reexamined the file submitted by the first applicant to approve a second entrant's application.

[70] The term 'new chemical entity' is understood broadly to mean a chemical compound not previously known or described. The IUPAC Recommendations (1998) define an NCE as "a compound not previously described in the literature", available at http://www.chem.qmul.ac.uk/iupac/medchem/ix.html

[71] An example of a bad practice is the US/Singapore FTA with "pharmaceutical chemical product" wording.

[72] By contrast, the U.S.-Central America Free Trade Agreement Countries requires member countries to provide five years of data protection from the date a product is given regulatory approval in their country. It also requires that member countries grant five years data exclusivity protections to originator companies if their product has received marketing approval anywhere in the world – even if the originator company has

6. Establish a mandatory registration period. A positive example is Chile. After ratification of the US/Chile FTA, the government of Chile passed a law[73] requiring that brand-name/originator drugs be registered within one year of U.S. approval in order to benefit from market exclusivity in Chile.

7. Clarify the existence of an early working exception that allows generic companies to initiate the application procedures and required studies during the data exclusivity term in order to start commercializing immediately after the expiry of the data exclusivity and patent terms.

8. Clarify that compulsory or government use licenses will include a compulsory license on underlying registration data, so that data exclusivities do not function as a barrier to compulsory licensing.

9. Create an exception for emergencies and public health crises.

not introduced the product in their country. Pharmaceutical companies may maneuver in this system to extend the period of monopoly control over the data to 10 years

[73] Ley No. 19.996, VIII, Article 91(e) (2005). Available (in Spanish) at: http://sdi.bcn.cl/boletin/publicadores/normas_publicadas/archivos/19996.pdf

POLICY PROPOSAL: Cost-Sharing Model for Pharmaceutical Test Data

Recognizing that several countries are facing U.S./ E.U. pressures to implement a TRIPS-plus model and reject the minimum non-disclosure model on the protection of their pharmaceutical test data, we advocate consideration of a particular approach to implementing TRIPS Article 39.3 obligation: a cost-sharing model for pharmaceutical test data.

The system we propose would provide compensation for data originators, which is not required by article 39.3 of the TRIPS Agreement. But for countries that cannot avoid TRIPS-plus obligations on the protection of pharmaceutical test data, the minimal TRIPS requirement of the nondisclosure approach is not a realistic option. For these countries, it is vital to identify other alternatives to the data exclusivity approach, and particularly to identify alternatives that address data exclusivity proponents' claims that generic firms unfairly free ride on the data generated by originators. In this context, we propose consideration of a model similar to that which the United States now uses for certain agricultural test data.

Background:

The U.S. system for agricultural test data involves a mandatory and automatic compulsory license on the originator's test data based on the principle of sharing the costs of originating the data, under the **Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA)**[74], an environmental protection law.

> The relevant provision reads in part:
>
> "The administrator (EPA) may, without the permission of the original data submitter, consider any such item of data (cited) in support of an application by another person ... if the applicant has made an offer to compensate the original data submitter. ... The terms and amount of compensation may be fixed by an agreement between the original data submitter and the applicant, or, failing such an agreement, binding arbitration….If, at the end of ninety days after the date of delivery to the original data submitter of the offer to compensate, the original data submitter and the applicant have neither agreed on the amount and terms of compensation nor on a procedure for reaching an agreement on the amount and terms of compensation, either person may initiate binding arbitration proceedings by requesting the Federal Mediation and Conciliation Service to appoint an arbitrator from the roster of arbitrators maintained by such Service. The procedure and rules of the Service shall be applicable to the selection of such arbitrator and to such arbitration proceedings, and the findings and determination of the arbitrator shall be final and conclusive, and no official or court of the United States shall have power or jurisdiction to review any such

[74] The FIFRA Act is available online at:
http://www.access.gpo.gov/uscode/title7/chapter6_subchapterii_.html

> findings and determination, except for fraud, misrepresentation, or other misconduct by one of the parties to the arbitration or the arbitrator where there is a verified complaint with supporting affidavits attesting to specific instances of such fraud, misrepresentation, or other misconduct. The parties to the arbitration shall share equally in the payment of the fee and expenses of the arbitrator.
> If the Administrator determines that an original data submitter has failed to participate in a procedure for reaching an agreement or in an arbitration proceeding as required by this subparagraph, or failed to comply with the terms of an agreement or arbitration decision concerning compensation under this subparagraph, the original data submitter shall forfeit the right to compensation for the use of the data in support of the application…..
> If the Administrator determines that an applicant (second) has failed to participate in a procedure for reaching an agreement or in an arbitration proceeding …., or failed to comply with the terms of an agreement or arbitration decision concerning compensation …., the Administrator shall deny the application or cancel the registration of the pesticide in support of which the data were used ….”
>
> 7 U.S.C. Chapter 6, Subchapter II, § 136a. Registration of pesticides
> FIFRA § 3(c)(1)(F)(iii)

How do the data-sharing provisions of the FIFRA work[75]?

1. In order to obtain marketing approval for some agricultural test data, originators provide the U.S. Federal Government with the data and the cost to generate the data (similar to the U.S. Orange Book obligations to submit patent information[76]). If the originators do not provide information on the cost of the data, they can face a negative presumption during the arbitration determination of the actual cost.

2. The originator gets ten years of market exclusivity, but for the 5 years afterward[77] the originator is granted a limited remuneration right subject to procedures for non-voluntary licenses by third parties.

3. During the 5 year period following the initial 10 years grant of exclusivity, Generic/second applications have an automatic right to use the data and can

[75] For an analysis of the FIFRA cost sharing model read M. Cresence Stanfford and James C. Wright: “Data Citation, Compensation and Cost Sharing: Pitfalls and Traps for the Unwary”. Available online at: http://www.pesticide.net/x/article/stafford20021210.pdf
[76] As described in the CPTech Discussion paper on linkage. See: “Patent-Registration Linkage” (CPTech Discussion Paper No. 2, 2006). Available online at: http://www.cptech.org/publications/CPTechDPNo2Linkage.pdf
[77] To be compensable, the study must have been submitted to EPA within fifteen years of being cited. A study may be cited and relied upon by another company, without any obligation to pay compensation, if it has been on file with EPA for more than fifteen years. (source: M. Cresence Stanfford and James C. Wright, supra note 75)

> register products relying on the data if they pay adequate remuneration to the test data originator.

The issue, of course, is what "adequate remuneration" is. The FIFRA system begins with a requirement for the generic entrant to attempt to resolve this issue voluntarily. Once the EPA (US Environmental Protection Agency) has issued a second entrant registration, the second applicant has to make an offer of compensation to the tests' originator, which becomes the starting point for a negotiation.

However, if the parties do not reach an agreement 90 days after the delivery of the offer[78] either party can request **binding arbitration**[79] with the Federal Mediation and Conciliation Service to establish compensation levels.

There is no explicit compensation standard set forth in FIFRA. However, since 1975 arbitration decisions have often been resolved based on a **cost-sharing approach,** meaning that the second applicant should share the cost of generating the test data with the originator.

The concrete allocation of costs between the parties is a controversial issue. The cost for the second applicant has sometimes been based upon their **relative/actual market share**[80], meaning that compensation is linked to the value of the data to each company, which depends on resulting sales. The argument is simple: if one party (A) has a market share larger than the other (B), (A) will benefit more than (B) from its registration; and since (A) can be expected to benefit more than (B), it should pay a proportionately larger share of the costs of the data development program.

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[78] Or **60 days** after a party offers to share the cost or jointly develop the data for FIFRA § 3(c)(2)(B)(iii) situations: "*If, at the end of sixty days after advising the Administrator of their agreement to develop jointly, or share in the cost of developing, data, the registrants have not further agreed on the terms of the data development arrangement or on a procedure for reaching such agreement, any of such registrants may initiate binding arbitration proceedings by requesting the Federal Mediation and Conciliation Service to appoint an arbitrator from the roster of arbitrators maintained by such Service. The procedure and rules of the Service shall be applicable to the selection of such arbitrator and to such arbitration proceedings, and the findings and determination of the arbitrator shall be final and conclusive, and no official or court of the United States shall have power or jurisdiction to review any such findings and determination, except for fraud, misrepresentation, or other misconduct by one of the parties to the arbitration or the arbitrator where there is a verified complaint with supporting affidavits attesting to specific instances of such fraud, misrepresentation, or other misconduct. All parties to the arbitration shall share equally in the payment of the fee and expenses of the arbitrator. The Administrator shall issue a notice of intent to suspend the registration of a pesticide ….if a registrant fails to comply with this clause*."

[79] For the official arbitration rules of FIFRA test data compensation/ cost sharing disputes (29 C.F.R. Part 1440) see: http://www.pesticide.net/x/cfr/arb_rule.htm

[80] For example, Dupont v. Griffin and Drexel/Docket No. 16-171-0080-86M (1988) Decision available at http://www.pesticide.net/x/comp/dupont1.htm. American Cyanamid v. Aceto / Docket No. 13-171-0800-85 (1989) Decision available at http://www.pesticide.net/x/comp/aceto.htm. Ciba-geigy v. Drexel Chemical / Docket No. 16 171 00321 92G (1994). Decision available at http://www.pesticide.net/x/comp/ciba.htm

The usual practice is that:

- The arbitration decides the amount of compensation and the second applicants' entrance into the market is not delayed, because the generic companies have an automatic right to use the data and these disputes are resolved while the generic product is on the market.

- Arbitration costs are shared equally between parties.

- Arbitration decisions may not be appealed, except for fraud, misrepresentation, or other misconduct by one of the parties or the arbitrator, where there is a verified complaint with supporting affidavits attesting specific instances.

- The basis for establishing compensation is the actual cost incurred by the originator, not how much it would cost to replace the data. The arbitrators require originators to provide evidence to support cost claims and the burden of proof is on the originator, since they are in a better position to know the actual cost of generating the data.

In at least one decision, a U.S. District Court has judicially confirmed a FIFRA final arbitration order[81]. In 1984, the U.S. Supreme Court reviewed the FIFRA data-sharing provisions on the Ruckelshaus case and declared that the provisions were constitutional and that there was no improper "taking" of property without just compensation.[82]

The proposal:

We propose that countries pressured in trade negotiations or other contexts to provide TRIPS-plus protection for pharmaceutical test data use a modified version of the FIFRA approach.

Under this system:

* Originators should be required to disclose their real investment costs in generating the test data and provide documentary evidence.

* The generic/second applicants should have an automatic right to use/rely upon the originators' test data from "day one" -- the first registration by the originator anywhere in the world -- and no data exclusivity periods should be applicable.

[81] U.S. District Court for the District of Columbia in Cheminova A/S v. Griffin L.L.C., 182 F. Supp. 2d 68 (D.D.C. 2002) available online at: http://www.pestlaw.com/x/comp/cheminova02.html

[82] Ruckelshaus v. Monsanto Co., 467 U.S. 986 (U.S. 1984). Some relevant language: "But Monsanto has not challenged the ability of the Federal Government to regulate the marketing and use of pesticides. Nor could Monsanto successfully make such a challenge, for such restrictions are the burdens we all must bear in exchange for the advantage of living and doing business in a civilised community."

* The originator of the test data would get a remuneration right during a limited period of time of 3 to 5 years. The generic/second applicants would contribute to the cost of generating this data by paying the originator an adequate and reasonable remuneration.

Again, determining the adequate remuneration is the key point. Two different approaches should be considered:

a) A "reasonable royalty" model, where generics could pay a percentage representing a modest share of the revenues on sales of the generic product.

b) A "pro-rata share of costs" model, where generics could pay a contribution based upon their share of the global market sales for the product.

This second option is similar to the one that some FIFRA arbitrators have designed for agricultural test data. A possible adjustment could be introduced for risk of investments and cost of capital[83]. The adoption of an arbitration system, similar to the one used for U.S. agricultural data, should also be considered for pharmaceutical data, in order to speed decision-making an avoid bogging down compensation determinations in the courts.

For the second option, it is essential that implementing legislation make it clear that a generic producer in a country would only be obligated to pay for the fraction of the total costs of the test data that is appropriate for their (likely small) fraction of the total global market for the product.

> For example, if the costs[84] of test data for a particularly drug were $50 million, amortized over five years in equal installments, and the generic producer had sales that were .1% of the **global market** for the product, the pro-rata share of the costs for one year would be as follows:
>
> $50,000,0000 x 1/5 x .001 = $10,000 (a year for 5 years)

If the domestic generic firm's share of the global market is smaller, the contribution will also be smaller.

Country-level determination of costs of conducting trials and generating test data might be assisted by international organizations, such as the World Intellectual Property Organization (WIPO) or the World Health Organization (WHO). These organizations could create a public database that would centralize the collection of data on the costs of the clinical trials worldwide. Such information might be collected in connection with a larger, public database that would include clinical test medical information.

[83] See, for example, the Microgen v. Lonza arbitration Decision (2000) available online at http://www.pesticide.net/x/comp/microgen3.html
[84] Calculated with appropriate adjustments for risk.

As compared to the data exclusivity approach, the proposed cost-sharing model has several **advantages**:

- During the period of protection, the test data originators can benefit from reasonable contributions to the costs of the test data -- without conferral of monopoly rents that overcompensate for the costs of generating data.

- Countries adopting this approach can resist demands to provide exclusive rights, because they are offering remuneration to drug developers based on their actual investment costs -- and thereby directly addressing the "free riding" criticism of the nondisclosure approach.

- National regulators can avoid the creation of monopolistic situations, and foster competition within the pharmaceutical industry.

- Generic competitors who share costs can enter the market without delay because there is no exclusive marketing period.

- Developing country generic companies' contributions will be affordable, because of their small share in worldwide sales.

- Generic competitors can enter the market during the period of data protection without unethically duplicating clinical trials by eliminating the need to duplicate clinical trials.

Criticisms of cost-sharing approach:

Some persons[85] have criticized the cost sharing approach for developing countries on the grounds that it represents a burden that is not required by the TRIPS Agreement, and also because it could be implemented in a manner that is complex or which leads to considerable litigation costs. The responses to these points are as follows.

First, if a country believes it can sustain a regime of no TRIPS plus rights in the test data, they can certainly do so. However, it is also true that faced with a choice between no economic rights and exclusive rights, many countries have adopted exclusive rights regimes. As a matter of strategy, a position of no-compromise may fail, a costly outcome for patients. One has to be realistic about feasible outcomes.

Second, while it is true that a regime can be implemented with complex rules or costly procedures, this is not at all necessary. The fact that rules for data are TRIPS plus means also that counties are free to design whatever rules they want, including rules that are very easy to follow, and inexpensive to administer. The U.S. approach to agricultural

[85] Among others: Initiative for Medicines, Access & Knowledge: "The Impact of Article 39.3 in India: A Practical Perspective" (2006, I-MAK); and B. Baker: "A critical analysis of India's probable data exclusivity/data compensation provisions" (2006, Health Gap), available at: http://www.cptech.org/blogs/ipdisputesinmedicine/2006/10/critical-analysis-of-indias-probable.html

data is a case in point, where decisions are made by arbitration, and appeals are not permitted. Very simple royalty schemes are also reasonable alternatives, which can be implemented without appeals, or with simple administrative appeals. In this regard, it is worth noting that all of the problems of determining remuneration levels and dealing with procedure are also an issue for compulsory licensing of patents. Indeed, the procedural rules for setting remuneration for test data can be much simpler than is the case for patents, because there are no TRIPS standards for doing so, unlike the case for patents under Article 31 of the TRIPS. Given the shorter term of a test data regime, and the ability to embrace systems of reasonable cost sharing or remuneration, the most important issue may be to ensure that generic entry is automatic, particularly when cost sharing or remuneration payments are modest, relative to prices of products.

Conclusion:

Countries all over the world are facing pressure to implement Article 39.3 of the TRIPS Agreement in ways that are harmful to consumer interests. The most harmful outcome is one that involves the granting of exclusive rights in test data -- an approach to be avoided whenever possible. Systems of remuneration and cost sharing for the use of test data are not yet practiced by developing countries, although many have accepted far worst outcomes, based upon exclusive rights. The choices between various approaches, including a regime that goes no further than that required by the TRIPS, will depend upon a country's assessment of both its self interest and the political feasibility of sustaining different approaches. The arguments against exclusive rights are strong, particularly as an exclusive rights regime for test data can be an even larger barrier to entry than a patent, and raises important issues concerning the unethical nature of repeating human medical experiments when the science is already known.

MODEL LANGUAGE FOR A COST-SHARING APPROACH[86]

1. Use of or Reliance on Undisclosed Test Data Submitted for Pharmaceutical Approval

Parties shall be permitted to use or rely on undisclosed data submitted by a prior party for the purpose of meeting government requirements for marketing approval of pharmaceuticals, or to have a government agency use or rely on the data. Such a right shall be automatic and is not subject to appeal.

2. Commercial Use of Undisclosed Test Data Submitted for Pharmaceutical Approval

[86] This model language was proposed in "A cost sharing model to protect investments in pharmaceutical test data" (CPTech Policy Brief No. 1, 2006) available online at http://www.cptech.org/publications/policybrief-no1-cost-sharing.pdf. For an earlier proposal see also R. Weissman: Data Protection: Options for Implementation. Included in the book: Negotiating Health: Intellectual Property and Access to Medicines, Pedro Roffe, Geoff Tansey, David Vivas-Eugui, Earthscan Publications Ltd. 2006.

When an agency requires parties, as a condition for the commercial marketing of pharmaceutical products which utilize new chemical entities, to submit undisclosed test or other data, the origination of which involves a considerable effort, the agency shall require subsequent applicants that use or rely upon the originator's data, or have the government use or rely upon such data for registration of competing products, to contribute to the costs of such tests, if the following conditions are met:

a. Marketing approval was obtained within the past five years.

b. Marketing approval was obtained within one year of any foreign approval.

b. The person who seeks contributions to the cost of such tests and data provides the agency with public disclosures of

i. the costs of such tests or data, supported by independent verification,
ii. a reasonable estimate of the country's likely share of the global market, and
iii. the amount of global revenue the product has generated to date, and in the previous 12 months.

3. Contributions to the cost of tests

a. Pursuant to section 2, parties using or relying, or seeking to have the government use or rely, on data submitted by a previous party shall make reasonable contributions to the costs of such data. The amount of the contribution shall be based upon the payment of a reasonable royalty for the use of the data, or payment of a pro-rata share of the adjusted costs of the data. In the absence of an agreement between the parties, the method and amount of payment shall be determined by the agency.

Reasonable royalty. If the reasonable royalty method is selected, the royalty rate should be either a rate agreed to by the parties, or 4 percent of the net sales of the generic product, or a different rate determined by the agency.

Pro-rata share of adjusted costs. If the pro-rata share method is selected, the adjusted cost shall be the actual costs, with reasonable and transparent adjustments for risks involved in clinical trials, based upon evidence of typical success rates for Phase I, II or III trials. The annual pro-rata share of the adjusted costs shall be one fifth of the total adjusted cost, multiplied by the generic company's percentage share of the global market for the product.

b. There shall be no compensation required where reliance on the data is sought for government or non-commercial purposes.

SOME RECOMMENDED READINGS:

C. Correa: Protecting Test Data for Pharmaceutical and Agrochemical Products under Free Trade Agreements (Included in the book: Negotiating Health: Intellectual Property and Access to Medicines, Pedro Roffe, Geoff Tansey, David Vivas-Eugui, Earthscan Publications Ltd. 2006).

J. H. Reichman: The international Legal Status of Undisclosed Clinical Trial Data: From Private to Public Goods? (Included in the book: Negotiating Health: Intellectual Property and Access to Medicines, Pedro Roffe, Geoff Tansey, David Vivas-Eugui, Earthscan Publications Ltd. 2006).

M. P. Pugatch: Intellectual Property, Data exclusivity, Innovation and Market Access (Included in the book: Negotiating Health: Intellectual Property and Access to Medicines, Pedro Roffe, Geoff Tansey, David Vivas-Eugui, Earthscan Publications Ltd. 2006).

R. Weissman: Data Protection: Options for Implementation (Included in the book: Negotiating Health: Intellectual Property and Access to Medicines, Pedro Roffe, Geoff Tansey, David Vivas-Eugui, Earthscan Publications Ltd. 2006).

MORE INFORMATION

Consumer Project on Technology
1621 Connecticut Ave, NW, Suite 500, Washington, DC 20009 USA
Tel.: +1.202.332.2670 Fax: +1.202.332.2673
www.cptech.org

Judit Rius Sanjuan
Staff attorney
judit.rius@cptech.org

And subscribe to IP-health:
http://lists.essential.org/mailman/listinfo/ip-health

ANNEX: RELEVANT U.S. LAW

FEDERAL FOOD, DRUG, AND COSMETIC ACT
***21 USCS § 355 New drugs*[87]**

New Drug Applications/ NDA/ Section 505(b)(2) applications

21 U.S.C. § 355(c)(3)(E)

(ii) If an application submitted under subsection (b) for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b), is approved after the date of the enactment of this clause [enacted Sept. 24, 1984], no application which refers to the drug for which the subsection (b) application was submitted and for which the investigations described in clause (A) of subsection (b)(1) and relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted may be submitted under subsection (b) before the expiration of **five years** from the date of the approval of the application under subsection (b), **except** that such an application may be submitted under subsection (b) after the expiration of four years from the date of the approval of the subsection (b) application if it contains a certification of patent invalidity or non-infringement described in clause (iv) of subsection (b)(2)(A). The approval of such an application shall be made effective in accordance with this paragraph except that, if an action for patent infringement is commenced during the one--year period beginning forty--eight months after the date of the approval of the subsection (b) application, the thirty--month period referred to in subparagraph (C) shall be extended by such amount of time (if any) which is required for seven and one--half years to have elapsed from the date of approval of the subsection (b) application.

(iii) If an application submitted under subsection (b) for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application approved under subsection (b), is approved after the date of the enactment of this clause [enacted Sept. 24, 1984] and if such application contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant, the Secretary may not make the approval of an application submitted under subsection (b) for the conditions of approval of such drug in the approved subsection (b) application effective before the expiration of **three years** from the date of the approval of the application under subsection (b) if the investigations described in clause (A) of subsection (b)(1) and relied upon by the applicant for approval of the application were not conducted by or for the applicant and if the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.

[87] Titles and emphasis added. Only most relevant sections included.

(iv) If a **supplement to an application** approved under subsection (b) is approved after the date of enactment of this clause [enacted Sept. 24, 1984] and the supplement contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the supplement and conducted or sponsored by the person submitting
the supplement, the Secretary may not make the approval of an application submitted under subsection (b) for a change approved in the supplement effective before the expiration of **three years** from the date of the approval of the supplement
under subsection (b) if the investigations described in clause (A) of subsection (b)(1) and relied upon by the applicant for approval of the application were not conducted by or for the applicant and if the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.

Abbreviated new drug application /ANDA

21 U.S.C. § 355(j)(5)(F)

(ii) If an application submitted under subsection (b) for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b), is approved after the date of the enactment of this subsection, no application may be submitted under this subsection which refers to the drug for which the subsection (b) application was submitted before the expiration of **five years** from the date of the approval of the application under subsection (b), **except** that such an application may be submitted under this subsection after the expiration of four years from the date of the approval of the subsection (b) application if it contains a certification of patent invalidity or non-infringement described in subclause (IV) of paragraph (2)(A)(vii). The approval of such an application shall be made effective in accordance with subparagraph (B) except that, if an action for patent infringement is commenced during the one--year period beginning forty--eight months after the date of the approval of the subsection (b) application, the thirty--month period referred to in subparagraph (B)(iii) shall be extended by such amount of time (if any) which is required for seven and one--half years to have elapsed from the date of approval of the subsection (b) application.

(iii) If an application submitted under subsection (b) for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application approved under subsection (b), is approved after the date of enactment of this subsection and if such application contains reports of new clinical
investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant, the Secretary may not make the approval of an application submitted under this subsection for the conditions of approval of such drug in the subsection (b) application effective before the expiration of **three years** from the date of the approval of the application under subsection (b) for such drug.

(iv) If a **supplement to an application** approved under subsection (b) is approved after the date of enactment of this subsection [enacted Sept. 24, 1984] and the supplement contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the supplement and conducted or sponsored by the person submitting the supplement, the Secretary may not make the approval of an application submitted under this subsection for a change approved in the supplement effective before the expiration of **three years** from the date of the approval of the supplement under subsection (b).

ANNEX: RELEVANT E.U. LAW

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[88]

OLD REGIME

Article 10 of the 2001/83/EC Directive:

"1. In derogation of Article 8(3)(i), and without prejudice to the law relating to the protection of industrial and commercial property:

(a) The applicant shall not be required to provide the results of toxicological and pharmacological tests or the results of clinical trials if he can demonstrate:

(i) either that the medicinal product is essentially similar to a medicinal product authorized in the Member State concerned by the application and that the holder of the marketing authorization for the original medicinal product has consented to the toxicological, pharmacological and/or clinical references contained in the file on the original medicinal product being used for the purpose of examining the application in question;

(ii) or that the constituent or constituents of the medicinal product have a well established medicinal use, with recognized efficacy and an acceptable level of safety, by means of a detailed scientific bibliography;

(iii) or that the medicinal product is essentially similar to a medicinal product which has been authorized within the Community, in accordance with Community provisions in force, for **not less than six years** and is marketed in the Member State for which the application is made. This period shall be extended to **10 years** in the case of high-technology medicinal products having been authorised according to the procedure laid down in Article 2(5) of Council Directive 87/22/EEC (1). Furthermore, a Member State may also extend this period to **10 years** by a single Decision covering all the medicinal products marketed on its territory where it considers this necessary in the interest of public health. Member States are at liberty not to apply the six-year period **beyond the date of expiry of a patent** protecting the original medicinal product.

However, where the medicinal product is intended for a different therapeutic use from that of the other medicinal products marketed or is to be administered by different routes or in different doses, the results of appropriate toxicological and pharmacological tests and/or of appropriate clinical trials must be provided.

[88] Titles and emphasis added. Only most relevant sections included.

(b) In the case of new medicinal products containing known constituents not hitherto used in combination for therapeutic purposes, the results of toxicological and pharmacological tests and of clinical trials relating to that combination must be provided, but it shall not be necessary to provide references relating to each individual constituent.

2. Annex I shall apply by analogy where, pursuant to point (ii) of paragraph 1, (a), bibliographic references to published data are submitted."

NEW REGIME

Article 6.1 of the 2001/83/EC Directive (after the 2004 Amendment):

"No medicinal product may be placed on the market of a Member State unless a marketing authorization has been issued by the competent authorities of that Member State in accordance with this Directive or an authorization has been granted in accordance with Regulation (EEC) No
2309/93.

When a medicinal product has been granted an initial marketing authorisation in accordance with the first subparagraph, any additional strengths, pharmaceutical forms, administration routes, presentations, as well as any variations and extensions shall also be granted an authorisation in accordance with the first subparagraph or be included in the initial marketing authorisation. All these marketing authorisations shall be considered as belonging to the same global marketing authorisation, in particular for the purpose of the application of Article 10(1)."

Article 10 of the 2001/83/EC Directive (after the 2004 Amendment):

"1. By way of derogation from Article 8(3)(i), and without prejudice to the law relating to the protection of industrial and commercial property, the applicant shall not be required to provide the results of pre-clinical tests and of clinical trials if he can demonstrate that the medicinal product is a generic of a reference medicinal product which is or has been authorised under Article 6 for **not less than eight years** in a Member State or in the Community.

A generic medicinal product authorised pursuant to this provision shall not be placed on the market until **ten years** have elapsed from the initial authorisation of the reference product.

The first subparagraph shall also apply if the reference medicinal product was not authorized in the Member State in which the application for the generic medicinal product is submitted. In this case, the applicant shall indicate in the application form the name of the Member State in which the reference medicinal product is or has been authorised. At the request of the competent authority of the Member State in which the application is submitted, the competent authority of the other Member State shall

transmit within a period of one month, a confirmation that the reference medicinal product is or has been authorised together with the full composition of the reference product and if necessary other relevant documentation.

The ten-year period referred to in the second subparagraph **shall be extended to a maximum of eleven years if**, during the first eight years of those ten years, the marketing authorisation holder obtains an authorisation for one or more **new therapeutic indications** which, during the scientific evaluation prior to their authorisation, are held to bring a significant clinical benefit in comparison with existing therapies.

2. For the purposes of this Article:
(a) "reference medicinal product" shall mean a medicinal product authorised under Article 6, in accordance with the provisions of Article 8;
(b) "generic medicinal product" shall mean a medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies. The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy. In such cases, additional information providing proof of the safety and/or efficacy of the various salts, esters, or derivatives of an authorised active substance must be supplied by the applicant. The various immediate-release oral pharmaceutical forms shall be considered to be one and the same pharmaceutical form. Bioavailability studies need not be required of the applicant if he can demonstrate that the generic medicinal product meets the relevant criteria as defined in the appropriate detailed guidelines.

3. In cases where the medicinal product does not fall within the definition of a generic medicinal product as provided in paragraph 2(b) or where the bioequivalence cannot be demonstrated through bioavailability studies or in case of changes in the active substance(s), therapeutic indications, strength, pharmaceutical form or route of administration, vis-à-vis the reference medicinal product, the results of the appropriate pre-clinical tests or clinical trials shall be provided.

4. Where a biological medicinal product which is similar to a reference biological product does not meet the conditions in the definition of generic medicinal products, owing to, in particular, differences relating to raw materials or differences in manufacturing processes of the biological medicinal product and the reference biological medicinal product, the results of appropriate pre-clinical tests or clinical trials relating to these conditions must be provided.
The type and quantity of supplementary data to be provided must comply with the relevant criteria stated in the Annex and the related detailed guidelines. The results of other tests and trials from the reference medicinal product's dossier shall not be provided.

5. In addition to the provisions laid down in paragraph 1, where an application is made for a **new indication for a well-established substance, a non-cumulative period of one year** of data exclusivity shall be granted, provided that significant pre-clinical or clinical studies were carried out in relation to the new indication.

6. Conducting the necessary studies and trials with a view to the application of paragraphs 1, 2, 3 and 4 and the consequential practical requirements shall not be regarded as contrary to patent rights or to supplementary protection certificates for medicinal products."

Article 10a of the 2001/83/EC Directive (after the 2004 Amendment):

"By way of derogation from Article 8(3)(i), and without prejudice to the law relating to the protection of industrial and commercial property, the applicant shall not be required to provide the results of pre-clinical tests or clinical trials if he can demonstrate that the active substances of the medicinal product have been in well-established medicinal use within the Community for at least ten years, with recognised efficacy and an acceptable level of safety in terms of the conditions set out in the Annex. In that event, the test and trial results shall be replaced by appropriate scientific literature."