

U.S and E.U Protection of Pharmaceutical Test Data¹

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Before a new drug is launched into the market, evidence of its safeness, effectiveness and quality must be provided to the national drug regulatory authorities. Normally this includes information from test and clinical trials involving human patients.

There are economic, practical and ethical reasons why second / generic entrants into the pharmaceutical market should not replicate the test data. The tests, particularly those involving human clinical trials, are expensive. The tests also may take several years to complete. Finally, it is unethical to replicate some testing of drugs on human subjects.

National drug regulatory authorities sometimes permit second entrant/generic applications to rely on the test data submitted by the originator/brand-name pharmaceutical company. This kind of approval only requires that the second entrant establish bio-equivalence with the originator drug, meaning that the generic version is metabolized the same way as the original version.

Article 39.3 of the TRIPS Agreement requires WTO Members States to protect pharmaceutical test data but only undisclosed test data originated from new chemical entities and that required considerable effort to generate.

TRIPS/ Section 7: Protection of Undisclosed Information³

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.”

¹ This work is licensed under the Creative Commons Attribution 2.5 License. To view a copy of this license, visit <http://creativecommons.org/licenses/by/2.5/> or send a letter to Creative Commons, 543 Howard Street, 5th Floor, San Francisco, California, 94105, USA.

² Helpful comments were received from Michael Palmedo and James Love.

³ Emphasis added

One of the key points in article 39.3 is that the obligation to protect is only from “unfair commercial use.” Some countries, for example Canada⁴, have determined that national drug regulatory authorities’ reliance on the originator test data to approve a generic product is not unfair commercial use and it is therefore not prohibited.

Recommended reading:

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#TopOfPage>

Influenced by their brand-name pharmaceutical industries, the United States and the European Union are urging countries to implement the article 39.3 obligation through a system of exclusive rights on pharmaceutical test data. The U.S./E.U. system goes considerably beyond the minimum obligations under the TRIPS and it is sometimes referred to as “**marketing exclusivity**” or “**data exclusivity**,”⁵ rather than the term “data protection.”

Before 1984 in the United States, and before 1987 in the European Union, pharmaceutical test data was protected as a **trade secret**. The basis for protecting trade secrets is unfair competition, that is competition based on dishonest practices. There was no legal prohibition against relying upon published data to establish 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 the current U.S. & E.U. exclusivity approach, generic drug manufacturers and national drug regulatory authorities cannot rely upon the 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 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 issue of data exclusivity has become especially relevant since the United States and the European Union are including requirements to recognize this practice in a variety of trade negotiations.⁶

⁴ Bristol-Myers Squibb Co. v. Canada (Attorney General), [2005] 1 S.C.R. 533, 2005 SCC 26 (CanLII). Available at: <http://www.ijcan.ca/ca/cas/scc/2005/2005scc26.html>

⁵ 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/or E.U. legal literature. Usually the term “marketing exclusivity” is more used in the U.S. regulatory system, and both the terms “data protection” and “data exclusivity” are more used in the E.U. system.

⁶ 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 US 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.

UNITED STATES⁷

Before 1984, the United States (U.S.) protection for an applicant's unpublished safety and efficacy data was basically a limited trade secret protection regime⁸.

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. 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 those cases, the generic company only had to prove bioequivalence with the product already on the market.

The 1962 amendments did not contain any provision for a separate approval process for drugs that were identical to drugs that had been 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 safety and efficacy requirements. The generic applicants were allowed to prove only bioequivalence 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. (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, applied to all antibiotic drugs approved under section 507 of the Federal Food, Drug, and Cosmetic Act.⁹

⁷ 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).

⁸ FDA regulations 21 CFR § 314.14 (f), codified in 1984 in the Section 21 U.S.C. § 355 (l).

⁹ Since an abbreviated approval process for generics already existed, such antibiotics were not included in the Hatch-Waxman provisions and were not eligible for patent-term extensions under the act. However, the

Drugs could also be approved based on a “**Paper**” **new drug application (NDA)**, in which applicant relied 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, and, moreover, nothing in the FDA regulations prevented the Agency from requesting additional studies or requests. According to one expert consulted, getting a paper NDA approved was an uncertain and expensive undertaking.

In 1984 a major pharmaceutical legislation reform took place with the **Drug Price Competition and Patent Term Restoration Act**¹⁰. This legislation is also known as the Hatch-Waxman Act.

The 1984 Hatch-Waxman Act effectively extended the Abbreviated New Drug Application (ANDA) processes that existed for antibiotics (and in certain ways 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 drug¹¹. The 1984 amendments also introduced a new kind of application: the 505(b)(2) applications¹².

Possible second applicants’ entrance into the U.S. Market: Since 1984, there are two possible ways a “second applicant” company can file for a 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 that allowed the reliance upon unpublished data, eliminated the need for FDA's paper NDA applications that permitted the approval of duplicate drugs through reliance upon published data.

Food and Drug Administration Modernization Act of 1997 made antibiotic drugs eligible for Hatch-Waxman extensions, thus increasing the returns from their development.

¹⁰ Pub. L. No. 98-417 (98th Congress, 1984)

¹¹ Abbreviated new drug applications (ANDA) are regulated in section 21 U.S.C. § 355(j). These are the typical generic applications. Application that contains 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.

¹² 505(b)(2) Applications are regulated in section 21 U.S.C. § 355(b)(2). These kinds of applications are for drugs that are only somewhat similar to another drug (e.g. the same composition but a new indication). Application 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>

The 1984 Hatch-Waxman Act also introduced several non-patent-marketing exclusivities regulations (see below). In this paper, we are going to focus in the so-called “**New drug product exclusivity**” or “**data exclusivity**”. The inclusion of the data 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 rights¹³. Two measures that were introduced to promote competition from the generic industry.

The current U.S. data exclusivity regulations are quite complex and co-exist with a number of other non-patent provisions that extend marketing exclusivities, including:

- Orphan drug exclusivity,
- Pediatric drug exclusivity,¹⁴
- Generic drug exclusivity,¹⁵
- 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 data exclusivity from the date of the FDA approval is granted to new drug products containing new chemical entities.

The main condition is that the approved new drug application must contain a new active ingredient that is a New Chemical Entity (NCE)¹⁶ or new active moiety¹⁷, never previously approved by the FDA alone or in combination.

¹³ Certain conducts related to obtaining FDA approval that would otherwise constitute patent infringement are exempted from infringement liability under the patent laws. 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”.

¹⁴ 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 (arguably a patent extension).

¹⁵ 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-days period of exclusivity. 21 USC 355 (j)(5)(B)(iv)(I)

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

The effect of this exclusivity is that no ANDA¹⁸ or 505(b)(2)¹⁹ applications may be submitted during the 5-year exclusivity period.

Note: 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.

There is an exception: 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 Certification²⁰).

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 sponsor that were essential to the approval of the application or the supplement.

The main conditions are that a new use/ indication is discovered and that the pharmaceutical company must have conducted or sponsored²¹ new clinical trials/investigations²² (other than bioavailability studies) which were essential for the

¹⁶ The FDA seems to interpret 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.

¹⁷ The FDA seems to interpret 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.

¹⁸ 21 U.S.C. § 355(j)(5)(F)(ii)

¹⁹ 21 U.S.C. § 355(c)(3)(E)(ii)

²⁰ Section 21 U.S.C. § 355(c)(3)(E)(ii): “...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).”

²¹ The FDA seems to interpret “conducted or sponsored” as 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.

²² The FDA interprets “new clinical investigation” as an investigation in humans, the results of which (1) have not been relied upon by FDA to demonstrate substantial evidence of effectiveness of a previously

approval of the new drug application or supplement.

For example, changes in an approved drug product that affect its active ingredients, strength, dosage form, route of administration or conditions of use may be granted exclusivity if clinical investigations were essential to approval of the application containing those changes.

Contrary to the five-year exclusivity, this three-year exclusivity allows the FDA to receive and review ANDA or 505(b)(2) applications before it 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.

Difference: Only a full new drug application can receive 5 years of exclusivity; while an application or a supplement to a new drug application can receive 3 years of exclusivity.

How does it work in practice?

1. The Center for Drug Research and Evaluation (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**²³, to find information on drugs that have received New Drug Product Exclusivity.

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 or delaying the submission of certain 505(b)(2) or ANDAs applications that rely in the originator’s test data.

Exclusivity has two different regimes: a) 5 years for drugs with new chemical entities; and b) 3 years for new uses/indications in already approved drug products, for which the originator conducted or sponsored new clinical investigations that were essential for the approval.

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 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.

²³ 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>

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

EUROPEAN UNION²⁴

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

Europe harmonized the medicinal products²⁵ marketing authorizations in 1965 with the Council Directive 65/65/EEC²⁶. The 1965 Directive established that a pharmaceutical company applying for a marketing approval should present results of test and clinical trials demonstrating its safety and efficacy.

The trade secret protection of the test data was not addressed in the 1965 Directive but it was not contemplated that such data could be directly used by the drug regulatory authorities to approve another drug. However, according to one of the references consulted, in 1984 the European Commission recognized the concept of "indirect use of such data" when 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".

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"²⁷ 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**²⁸, which amended the 65/65/EEC Directive.

²⁴ For some background reading: 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)

²⁵ In E.U. terminology, "pharmaceutical products" are referred as "medicinal products".

²⁶ 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

²⁷ In Europe, "Abridged applications" are the applications where, subject to certain conditions, the applicant is 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.

The 1987 Directive, as well as several others, was consolidated in 2001 in a single **Community Code**, the Directive 2001/83/EC²⁹.

The 1987 Directive also introduced a new harmonized procedure for abridged applications for “essentially similar” products, the classic generic applications³⁰. Since 1987 European second/generic applicants for medicinal products that show that their product is “essentially similar” to a product already authorized can rely³¹ 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 the Generics case³², the European Court of Justice (ECJ) defined what should be understood by “essentially similar” medicinal product: “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”.

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

As explained, the essentially similar abridged procedure is the typical application for generic products.

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”³³.

As it 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 expired³⁴.

²⁸ 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

²⁹ 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

³⁰ 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.

³¹ 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.

³² C-368/96 Generics (UK) and Others [1998] ECR I-1967

³³ Regulated in second subparagraph of Article 10.1(a)(iii) of the Directive 2001/83/EC

The “Published Literature Exemption”, when the second applicant presents references to published scientific literature demonstrating that the product “have well established medicinal uses”, is also a possibility³⁵. After the Scotia³⁶ and the Taxol³⁷ litigations, the exemption was amended and now the E.U. legislation establishes³⁸ that the period of time required for establishing a well-established use of a constituent of a medicinal product must not be less than one decade from the first systematic and documented use of that substance as a medicinal product in the E.U.

At the time, the introduction of a 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 pharmaceuticals³⁹ and that were faced with the introduction of the described new procedure for “essentially similar” abridged applications.

In July 2001 the E.U. launched an initiative to revise key aspects of the pharmaceutical legislation; data exclusivity being one of the key topics. The result was the **2004/27/EC Directive**⁴⁰ that amended Directive 2001/83/EC. Member States had until October 30, 2005 to implement the new revised Directive. From that date, the Directive applies immediately but the new data protection harmonized periods will benefit only drugs which are submitted for authorization after the implementation date, 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.

Therefore it is necessary, to study both regimes, the present and the future; but before some background information:

³⁴ 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.

³⁵ 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.

³⁶ 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

³⁷ Bristol-Myers Squibb BV v. Het College ter Beoordeling Van Geneesmiddelen (Medicines Evaluation Board) and Yew Tree Pharmaceuticals BV. Utrecht District Court, 2000

³⁸ Article 10a of the Directive 2001/83/EC, as amended

³⁹ 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.

⁴⁰ 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

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
- b) Mutual recognition procedure (decentralized) to approve medicinal products that will be marketed in several Member States.
- c) London-based European Medicines Agency (EMA) Centralized procedure⁴¹ to approve "eligible" medicinal products⁴². 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) The Present: 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 and there are four different lengths of exclusivity:

- a ten-year mandatory period: for high-tech medicinal products that are approved by the EMA through the centralized procedure.
- a six-year minimum period⁴³: 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 duration⁴⁴: Member States that apply the six-year minimum period may choose to cap this period at the instant the patent protecting the drug expires.

⁴¹ 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

⁴² 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.

⁴³ 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.

⁴⁴ Greece, Spain, and Portugal have opted for this solution

- a ten-year optional period⁴⁵: based on a finding that it is “necessary in the interest of public health” Member States can decide to extend the six-year period of protection up to a ten-year ceiling to all eligible pharmaceuticals marketed on their territory, discrimination on the basis of the country of origin is prohibited.

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 schedules⁴⁶ or formulations⁴⁷.

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 before approved.

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 they have to wait for expiry before filing their application. The European Generic Medicines Association (EGA) position is that “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”⁴⁸.

In a few words: 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) The Future: Directive 2001/83/EC (as amended by Directive 2004/27/EC)

The new 2001/83/EC Directive⁴⁹ introduces a **harmonized "8+2+1" formula** for new drugs approved either through the centralized procedure or the mutual recognition procedure.

⁴⁵ Belgium, Germany, France, Italy, The Netherlands, Sweden, the United Kingdom, and Luxembourg have opted for this solution.

⁴⁶ 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”)

⁴⁷ 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”)

⁴⁸ Available at: <http://www.egagenerics.com/gen-dataex.htm>

⁴⁹ A not official consolidate version is available at: http://pharmacos.eudra.org/F2/eudralex/vol-1/CONSOL_2004/Human%20Code.pdf

The new E.U. pharmaceutical legislation has created an **eight-year Data Exclusivity**, starting with the initial approval of the “European reference medicinal product”⁵⁰ + **two-year Market Exclusivity**. 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 rules⁵¹ and therefore there is no data protection for these changes⁵².

In practice, the second/generic applicant can file its request for a marketing authorization after eight years, but has to wait two or three more years before the authorization is made effective. Therefore, the second applicant cannot place its drug on the market before ten or eleven years have elapsed, starting from with the initial approval of the reference medicinal product⁵³.

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 others new therapeutic indications with a significant clinical benefit.

Other Data Exclusivity Regimes:

The European revised legislation also provides that:

a) "Well-established"/old products are entitled to receive a one-year data protection period if they are granted approval for a new therapeutic indication. Contrary to new

⁵⁰ 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.

⁵¹ Article 6.1 of the Directive 2001/83/EC, as amended.

⁵² 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).

⁵³ See chart and summary from the European Generic Medicines Association. Available at: <http://www.egagenerics.com/gen-dataex.htm>

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 ie, 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".

b) The 2004 Directive also recognizes one-year data exclusivity provision 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 procedure⁵⁴.

⁵⁴ 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/hums/human/biosimilar/biosimilarfin.htm>

COMPARATIVE

	WTO TRIPS	United States⁵⁵	European Union⁵⁶ (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)

⁵⁵ Federal Food, Drug and Cosmetic Act – USC 355

⁵⁶ 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 the access to affordable medicines.
- There is no obligation in the TRIPS 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 exportation of the U.S. Hatch-Waxman regime to other countries with very different income and needs has been strongly criticized by one of its proponents, Representative Henry A. Waxman.⁵⁷
- It is a form of double protection, since the 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 both unethical and wasteful to ask for duplication of clinical trials.
- Unless the exclusive rights in the data can be overridden, it can make compulsory licenses of patents or government use orders ineffective.
- It undermines the Bolar/ Early Working patent exception which seek to encourage quick access to the post patent market for generic medicines by exempting from patent liability certain conducts. 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.

⁵⁷ 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>

RECOMMENDATIONS:

The general recommendation is that countries should not include data exclusivity/marketing exclusivity provisions into the national law. As explained above, the TRIPS agreement does not require it. Article 39.3 only requires countries to protect test data against “unfair commercial uses”, not against practices required or permitted by the law, such as generic applications that rely on previously approved product.

However, if some type of protection is required, for example as a consequence of trade agreements with the United States or the European Union, there are several actions that can be taken to reduce its negative effects:

1. Short period of protection: there is no TRIPS obligation to impose five or ten year terms of protection⁵⁸.
2. Protection only to undisclosed data, not to data that is already published or publicly available⁵⁹.
3. Protect only the test data for which submission was required by the national authority and relied on. Therefore, if the national authority relies upon an approval granted in a foreign country, the obligation of protection should not apply⁶⁰.
4. Protection should be provided only to “New Chemical Entities” (NCE), not to new uses/indications.
5. A restrictive definition of NCE⁶¹ is necessary: molecules that were not previously incorporated within a product or published; excluding second indications, new formulations or dosage forms⁶².
6. It is also important to have a worldwide definition of NCE, “the data exclusivity period starts at the time the originator drug is approved in a party to the

⁵⁸ 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 member states are free to determine a period of protection that they consider in accordance with their national interest.

⁵⁹ Examples of bad practices are the US/Singapore and US/Morocco FTA where there is a reference to submission of “information” without qualification. And also the US/CAFTA.

⁶⁰ 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.

⁶¹ The term ‘new chemical entity’ is understood broadly to mean a chemical compound not previously known or described. Glossary of Terms Used in Medicinal Chemistry (IUPAC Recommendations 1998) <<http://www.chem.qmul.ac.uk/iupac/medchem/ix.html>> which defines an NCE as ‘a compound not previously described in the literature’.

⁶² An example of a bad practice is the US/Singapore FTA with “pharmaceutical chemical product” wording.

- agreement” is a better standard than “at the time is approved in the developing country”⁶³.
7. Clarify the existence of an early working exception allowing the 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. Establish a mandatory registration period. A positive example is Chile: after the ratification of the US/Chile FTA, the government of Chile passed a law⁶⁴ requiring that brand-name/originator drugs be registered within one year of U.S. approval in order to benefit from market exclusivity in Chile.

Alternative Proposal: a Cost Sharing Model

When negotiating trade agreements and/or considering modifications in national regulations, non-U.S. or E.U. models for pharmaceutical test data protection should be considered.

Recognizing that several countries are facing U.S./ E.U. pressures to implement a TRIPS Plus model and reject the minimum Non-disclosure/Non-appropriation model on the protection of their pharmaceutical test data; CPTech presents a particular approach to implementing TRIPS Article 39.3 obligation.

For more information: “A Cost Sharing Model to Protect Investments in Pharmaceutical Test Data”. CPTech Policy Brief No. 1 (2006). Available at: <http://www.cptech.org/publications/policybrief-no1-cost-sharing.pdf>

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

⁶³ An example of a bad practice is the US-CAFTA with NCE limited to entities not previously approved in the same party.

⁶⁴ Ley No. 19.996, VIII, Article 91(e) (2005). Available (in Spanish) at: http://sdi.bcn.cl/boletin/publicadores/normas_publicadas/archivos/19996.pdf

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

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ANNEX: RELEVANT U.S. LAW

FEDERAL FOOD, DRUG, AND COSMETIC ACT
21 USCS § 355 New drugs⁶⁵

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.

⁶⁵ 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 USE⁶⁶

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.

(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.

⁶⁶ Titles and emphasis added. Only most relevant sections included.

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.”