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Drug Marketing Exclusivity Under United States and European Union Law

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I. INTRODUCTION

The pharmaceutical industry is comprised of pioneer and generic companies; while the former develop and market new drugs, the latter copy them and sell them at reduced prices.[1] Generic companies can enter the market only when the various protections sheltering the pioneer drug have expired. The most important of these protections undoubtedly is the one conferred by a patent, but patents are not the only protection against generic competition: nonpatent exclusivity plays an increasingly important role.

Briefly stated, a marketing exclusivity[2] confers a pioneer company a limited protection against competitors. It prevents—during a set period of time—a second pharmaceutical applicant from obtaining a marketing authorization for its drug (this applicant is hereinafter also referred to as the "second entrant"[3]) through a facilitated procedure; this procedure entails reliance by this second applicant on preclinical and clinical data generated by a pioneer company that prepared that data to support its own new drug

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[1] Because generic manufacturers can obtain marketing approval without engaging in significant research and development (R&D) expenditures (e.g., preclinical and clinical studies), they are able to set a price lower than what the innovator company would charge in order to recoup its own expenditure.

[2] 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. This article uses the term "marketing exclusivity" to refer to the U.S. regulatory system, and both the terms "data protection" and "data exclusivity" to refer to the E.U. system.

[3] The term "second applicant/second entrant" is chosen to encompass both a company filing 1) a generic a application (in the United States, called an abbreviated new drug application (ANDA), according to 21 U.S.C. § 355(j); and 2) a new drug application (NDA) pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) (in Europe, the equivalent application is called an hybrid abridged application).

The difference between a 505(j) generic ANDA and a 505(b)(2) NDA is an important one to grasp. ANDAs are the "classic" applications for generic drugs that are identical or almost identical to the pioneer reference drug. In contrast, 505(b)(2) NDAs are used for drugs that are only somewhat similar to another drug (e.g., the same composition but a new indication). Both 505(j) generic ANDAs and 505(b)(2) NDAs imply reliance (in full or in part) on the data prepared by a third party, usually the sponsor of the reference (pioneer) drug. 505(b)(2) applications can rely on data originating from more than one pioneer application. On the similarity requirements applicable to a 505(j) application, see, e.g., *Zeneca v. Shalala*, 213 F.3d 161 (4th Cir. 2000). The U.S. Food and Drug Administration (FDA) has enacted a draft guidance to clarify how it interprets the 505(b)(2) requirement. Center for Drug Evaluation and Research (CDER), FDA, Applications Covered by Section 505(b)(2), Draft Guidance, at 12 (Oct. 1999), *available at* http://www.fda.gov/cder/guidance/2853dft.pdf (last visited Feb. 15, 2005) [hereinafter FDA, 505(b)(2) Draft Guidance]. This Guidance has been very controversial and has been attacked by the brand-name industry through citizen petitions. *See, e.g.*, Citizen petition of Morgan, Lewis & Bockius (on behalf of Pfizer) to FDA (July 27, 2001), *at* http://www.fda.gov/ohrms/dockets/dailys/01/Jul01/073001/cp00001.pdf; comments by the Generic Pharmaceutical Association (GPhA) to FDA (Oct. 9, 2003), *at* http://www.fda.gov/ohrms/dockets/dailys/03/oct03/101403/02p-0447-c000003-vol2.pdf. So far, FDA has defended its interpretation and guidance.

application (NDA). Because the drug for which the second applicant requests marketing approval is identical or similar to the first drug (hereinafter called the "reference" or the "pioneer" drug[4]), the latter's marketing application is relevant to assess the second entrant's application. Yet, marketing exclusivity limits the possibility of using the pioneer's data to evaluate the second application. During the limited period of exclusivity, the second entrant can obtain marketing approval only if it generates its own data supporting the safety and efficacy of its drug. Because the process of generating the requisite data is extremely costly, most second entrants—and particularly generic manufacturers—prefer to wait for the expiry of the marketing exclusivity rather than undertaking this expense. The practical consequence is to postpone the second applicant's market entry; in particular, generic competition is delayed for the duration of marketing exclusivity.[5]

Greg Perry, Director General of the European Generic Medicines Association (EGA), has fittingly highlighted the importance of nonpatent exclusivity:

> For originator pharmaceutical companies, the expansion of data exclusivity provisions has become one of the main ways of extending market protection and blocking generic competition. Data exclusivity is seen now as the principal means of extending market protection for new indications, pharmaceutical forms and other variations, especially where these are not innovative enough to gain patent protection.[6]

This article concentrates exclusively on marketing exclusivity (called "data protection" or "data exclusivity" in Europe); orphan, pediatric, and generic exclusivities are outside its scope. The article starts by explaining the context in which marketing exclusivity has been introduced; both its economic and its practical justifications are reviewed. Part III describes the requirements to be fulfilled to receive marketing exclusivity under U.S. law. Part IV presents the corresponding analysis under E.U. law; both current and future E.U. regulations are considered, given that the European Union

[4] FDA defines the "reference listed drug" as the drug "identified by FDA as the drug product upon which an applicant relies in seeking approval of its abbreviated application." *See* FDA, 505(b)(2) Draft Guidance, *supra* note 3. Among listed drugs, FDA chooses which is the reference listed drug, to which all generic applications will refer. When several listed drugs can be considered, FDA will select, as the reference listed drug, the "market leader … on the basis of commercial data." FDA, Abbreviated New Drug Application Regulations (Final Rule), 57 Fed. Reg. 17,950 (Apr. 28, 1992) [hereinafter FDA, 1992 ANDA Final Rule].

[5] Generic manufacturers also have to wait for the expiry of the patent(s) covering the pioneer drug. Rare is the drug protected only by *one* patent; to the contrary, "[a] major medicine may have over 30 patents." European Generic Medicines Association (EGA), Making Medicines Affordable, Data Exclusivity New Threat to Affordability, No. 3 (2002), *at* http://www.pharmalaw.org/EGA%20documents%20(pdf)2.pdf (last visited Feb. 24, 2005) [hereinafter EGA, New Threat to Affordability].

[6] Greg Perry, *Data Exclusivity—A Major Threat to Access to Affordable Medicines*, BUSINESS BRIEFING: PHARMAGENERICS 2002, at 16. The same idea was rephrased, albeit in a more positive light, by Harvey Bale, Director General of the International Federation of Pharmaceutical Manufacturers Associations (IFPMA): "[I]ntellectual property is essential. However, patent and trademark protection are not the entire story. This paper corrects for the relative lack of attention given to another important component essential for continued therapeutic progress—the protection of crucial information generated by painstaking analysis in the drug and vaccine development process." INTERNATIONAL FEDERATION OF PHARMACEUTICAL MANUFACTURERS ASSOCIATIONS (IFPMA), ENCOURAGEMENT OF NEW CLINICAL DRUG DEVELOPMENT—THE ROLE OF DATA EXCLUSIVITY (2000), *at* http://www.irpma.org.tw/english/doc/IFPMA-Encouragement%20of%20new%20clinical%20drug%20development-the%20rold%20of%20Data%20Exclusivity.pdf (last visited Feb. 15, 2005) [hereinafter IFPMA, ENCOURAGEMENT].

completed in spring 2004 the revision of its Directive governing data exclusivity. The article concludes by observing that the regulatory system of marketing/data exclusivity should be better tailored to balance the conflicting interests it is supposed to take into account.

II. CONTEXT

A. *Justification for Marketing Exclusivity*

Research-based pharmaceutical companies invest between $110 million[7] (low estimate) and $880 million (high estimate) to bring a single new drug product to the market.[8] The average preclinical and clinical development lasts ten years.[9] But once a drug finally is approved, competitors could copy it at a very low cost and sell it at a much reduced price if it were not for patent protection. Sponsors of pioneer drugs therefore seek to obtain the broadest patents for their drugs. A patent protects an invention,[10] which must be novel,[11] nonobvious[12] and capable of industrial applications.[13] For twenty years (starting on the day of the patent application),[14] products incorporating the patented invention are protected against copy by unauthorized parties. If the patented drug also has received marketing approval in the country[15] that issued the patent, only the patent holder (and its approved licensees) can sell it there for the duration of the

[7] This number corresponds to the after-tax cash outlays. PUBLIC CITIZEN, RX R&D MYTHS: THE CASE AGAINST THE DRUG INDUSTRY'S R&D "SCARE CARD" 3 (July 2001), *at* http://www.citizen.org/documents/ACFDC.PDF (last visited Feb. 15, 2005).

[8] *See* Joseph A. DiMasi et al., *The Price of Innovation: New Estimates of Drug Development Costs*, 22(2) J. HEALTH ECON. 151-85 (2003); Tufts Center for the Study of Drug Development, Backgrounder: A Methodology for Counting Costs for Pharmaceutical R&D (Nov. 1, 2001), *at* http://csdd.tufts.edu/NewsEvents/RecentNews.asp?newsid=5 (last visited Feb. 15, 2005); BOSTON CONSULTING GROUP, A REVOLUTION IN R&D, HOW GENOMICS AND GENETICS ARE TRANSFORMING THE BIOPHARMACEUTICAL INDUSTRY 6 (Nov. 2001), *at* http://www.bcg.com/publications/files/eng_genomicsgenetics_rep_11_01.pdf (last visited Feb. 15, 2005); PHARMACEUTICAL RESEARCHERS AND MANUFACTURERS OF AMERICA (PHRMA), INDUSTRY PROFILE 2003, ch. 1, at 2 ("The average cost to develop a new drug has grown from $138 million in 1975 to $802 million in 2000."), *at* http://www.phrma.org/publications/publications/profile02/2003%20CHAPTER%201.pdf (last visited Feb. 15, 2005).

[9] According to a study by Centre for Medicines Research (CMR), "total development times, from synthesis to first world launch" lasted thirteen years for new chemical entities (NCEs) in 1999. Malcolm Ogg, CMR, *Major Challenges for the Pharmaceutical Industry in the New Millenium*, *at* http://www.cmr.org/pdf/CMR00-137R_PIO_99_Briefing.pdf (last visited Feb. 24, 2005).

[10] In the United States, 35 U.S.C. § 101-103. In Europe, Art. 52 of the European Patent Convention. In the important case of *Feist Publications*, the U.S. Supreme Court denied copyright protection to compilation of data, considering that mere "sweat of the brow" does not replace the originality requirement. Feist Publications v. Rural Tel. Serv. Co., 499 U.S. 340 (1991). Hence, clinical data cannot be protected by copyright. In the European Union, databases are given protection under Directive 96/9/EC of 11 March 1996 on the Legal Protection of Databases, *available at* http://europa.eu.int/smartapi/cgi/sga_doc?smartapi!celexapi!prod!CELEXnumdoc&lg=en&numdoc=31996L0009&model=guichett (last visited Feb. 15, 2005).

[11] In Europe, Art. 54 of the European Patent Convention. The text of the Convention is *available at* http://www3.european-patent-office.org/dwld/epc/epc_2002_v1.pdf (last visited Feb. 15, 2005).

[12] As per Art. 56 of the European Patent Convention, the invention must incorporate an inventive step, a condition that is satisfied if the invention is not obvious to a person skilled in the art.

[13] Art. 57 of the European Patent Convention.

[14] 35 U.S.C. § 154(a)(2).

[15] Grants of patent rights and of marketing approvals are normally decided on a national basis, except that the European Union also operates a centralized regional system for drug approval. Different administrative authorities are responsible for patent grants and for marketing approval decisions.

patent.[16] The patent holder thus enjoys a monopoly, constrained only by the availability of other drugs belonging to the same therapeutic class.

Patent and marketing exclusivities are awarded independently.[17] For instance, the drug's patent may expire or be ruled invalid before marketing approval and marketing exclusivity are granted. Similarly, if a valid patent covers the pioneer drug, it effectively prevents generic entry, whether or not a marketing exclusivity period is running.[18]

Given the extent of patent protection, why is there a need for marketing exclusivity? This subpart seeks to answer the question by considering the various justifications for marketing exclusivity.

1. *To Encourage Pharmaceutical Research*

What happens when a pharmaceutical company has a potentially-promising drug candidate in its pipeline, but comes to realize that the drug cannot be patented? Understandably, the company will be reluctant to invest further in this drug.[19] This reluctance is rational because the lack of patent protection permits immediate copying by generic competitors.[20] It nonetheless represents a case of market failure; had the drug been marketed, it would have satisfied a consumer demand. It may have saved or improved lives or it may have led to significant savings in other healthcare sectors (e.g., reduced hospital stays).

To address this unsatisfactory situation and to encourage pharmaceutical research and development (R&D) when existing incentives are not sufficient, governments either can set a lower threshold for patent protection or grant alternative (i.e., nonpatent) forms of protection; they also may cumulate the two.[21] Marketing exclusivity represents one of these possible alternatives intended to encourage innovation. As can be expected, generic firms and pharmaceutical companies disagree as to the precise role that marketing exclusivity ought to play.

a. *Incentive for Innovation?*

According to the generic industry, drug R&D deserves to be encouraged only if its outcome (i.e., a new pharmaceutical product) meets the condition of patentability. In its view, only truly innovative outcomes warrant reward.[22] Consequently, innovative drugs

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[16] The patent holder can decide to issue patent licenses to selected third parties, who then also can sell the patented drug. *See, e.g.,* Alfred B. Engelberg, *Special Patent Provisions for Pharmaceuticals: Have They Outlived Their Usefulness?*, 39 J.L. & TECH. 389, 393 (1999).

[17] *See, e.g.,* Organon v. Teva, 244 F. Supp. 2d 370, 373 (D.N.J. 2002).

[18] A patent does not necessarily block the marketing of a rival product approved following the 505(b)(2) route. On 505(b)(2) applications, see *supra* note 3.

[19] A brand-name company applies for a patent many years before its drug is to reach the market. To do otherwise would have resulted in the intolerable risk that the information would become generally known and thereby preclude the grant of any patent at a later date. More importantly, the early issuance of a patent containing broad claims serves to discourage potential competitors from investing in research involving similar compounds.

Engelberg, *supra* note 16, at 394.

[20] The generic company starts to prepare its application long *before* the patent on the pioneer drug has expired. "In a typical generic product development cycle, a generic company commits resources to target a product three to five years before the originator patent expires. […] Often generic companies begin preparations to compete about seven years before the patent expires or exclusivity ends." Richard J. Findlay, *Originator Drug Development*, 54 FOOD & DRUG L.J. 227, 229 (1999).

[21] One possibility would be to loosen the nonobviousness/inventive step requirement and to allow a patent to issue simply on new concepts.

[22] According to Greg Perry, "If product variations or new uses cannot gain patent protection because they cannot demonstrate novelty and inventive step, it is simply wrong that they should be able to obtain market protection 'through the back door' by gaining data exclusivity." EGA POSITION PAPER, DATA EXCLUSIVITY: A MAJOR OBSTACLE TO INNOVATION AND COMPETITION IN THE E.U. PHARMACEUTICAL SECTOR 6 (Dec. 2000) [hereinafter EGA, MAJOR OBSTACLE], *available at* http://www.egagenerics.com/doc/ega_dataex-2000-12.pdf (last visited Feb. 24, 2005).

have no need for marketing exclusivity because they already can benefit from a twenty-year patent; marketing exclusivity mainly is of use to drugs that lack the innovative features required by patent law.[23] The marketing exclusivity system encourages drug development targeted toward product line extensions (e.g., slow release versions of pre-existing drugs).[24] For the generic industry, this incentive operates to divert resources away from more important research (e.g., drugs addressing unmet medical needs or drugs with life-saving potential).[25] The generic industry stresses that no scientific study has demonstrated that marketing exclusivity provides targeted incentives for socially-productive research. To buttress its point, the industry adds that, although the United States has shorter periods of exclusivity than the European Union, its innovative capacity is far above that of Europe.[26]

The position of the generic industry is too extreme. First, it has not established that the value of a noninnovative drug is necessarily and significantly lower than the value of an innovative (and hence normally patentable) product. For example, developing a simpler dosage form may help reduce medication errors;[27] it is a valuable addition to the therapeutic arsenal even though it is not innovative *per se*.[28]

Second, marketing exclusivity does provide a beneficial incentive because pharmaceutical companies are not always able to predict with accuracy whether their early investments ultimately will lead to a valid and strong patent. This uncertainty would deter research in both innovative and less cutting-edge areas if marketing exclusivity did not extend its "safety net." In other words, by denying marketing exclusivity to all noninnovative/unpatentable research outcomes, one runs the risk of discouraging drug R&D that could have led to innovative/patentable products.[29]

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[23] *Id*.

[24] According to a 1999 CMR study, a third of R&D expenditures at large pharmaceutical companies is devoted to line extensions. *See* Ogg, *supra* note 9. On the benefits of line extensions, see also Joseph DiMasi & Cherie Paquette, *The Economics of Follow-on Drug Research and Development*, 22(2) PHARMACOECONOMICS 1-14 (2004), *at* http://www.who.int/intellectualproperty/submissions/en/Submission_DiMasi.pdf.

[25] The European generic industry considers that the "causal link between data exclusivity and encouraging innovation" has not been established; moreover, "widening data exclusivity provisions would undermine genuine innovation in the [European Union], since it would encourage originator companies to focus their activities on product changes, rather than focus on developing new innovative and beneficial products." EGA, MAJOR OBSTACLE, *supra* note 22.

[26] EGA, New Threat to Affordability, *supra* note 5.

> Over the past 10 years, R&D investments have increased almost fivefold in the United States, about twice as fast as in Europe. … In 1999, European companies spent only 59 percent of their worldwide R&D in the EU, down from 73 percent in 1990. The United States was the main beneficiary of this shift in R&D expenditures. … 8 of the top 10 worldwide prescription drugs by sales originate in this country, compared to 2 from Europe.

PHRMA, INDUSTRY PROFILE 2003, *supra* note 8, at 16 (text available at http://www.phrma.org/publications/publications/profile02/2003%20CHAPTER%202.pdf (last visited Feb. 24, 2005)). Of course, there may be factors other than the duration of marketing exclusivity to explain why U.S. drug research is more successful than European research.

[27] *See* Timothy S. Lesar, *Medication Errors Related to Dosage Formulation Issues*, 2(2) MEDSCAPE PHARMACISTS (2001), *at* http://www.medscape.com/viewarticle/408579_print (registration required) (last visited Feb. 15, 2005).

[28] The research-based industry emphasizes the value of what it calls "sequential innovation." *See, e.g.,* Gregory J. Glover, Competition in the Pharmaceutical Marketplace, Statement PhRMA, before the Federal Trade Commission (FTC) and the Dep't of Justice 2 (Mar. 19, 2002), *at* http://www.ftc.gov/opp/intellect/020319gregoryjglover.pdf (last visited Feb. 15, 2005).

[29] The extent of this threat depends in part on how early the pharmaceutical firm introduces patent considerations in its investment decisionmaking process, and at what point in the development process does it realize that its compound ultimately will not be patentable. Pharmaceutical R&D also involves staged investments spread throughout a long period; thus, at each of these stages the pharmaceutical company reassesses the economic viability of its R&D drug projects.

Finally, the reasoning of the generic associating patent with innovation is overly simplistic. A brand-name company can lose its patent (or its right to a patent) even though its drug was innovative in the first place. For example, a patent may be denied or held invalid because the inventor made the mistake of publishing its discovery before applying for the patent.[30] Marketing exclusivity partially offsets this risk, because once an exclusivity is granted it offers a very strong protection.[31]

b. *Marketing Exclusivity: A Cheaper Alternative to Patent?*

Until the mid-1980s, pharmaceutical inventions achieved by noncommercial entities (e.g., the National Institutes of Health (NIH) or universities) were left largely unpatented.[32] Because patents are costly to obtain and to maintain, these institutions were reluctant to apply for one whenever their invention's commercial prospects were uncertain. In contrast, marketing exclusivity comes into force only once the invention has proven its usefulness as a safe and effective drug. Compared to a patent, it entails significantly less administrative and procedural burden; it also is cheaper to obtain and to maintain (e.g., no patent attorney to pay to prepare an application, and no maintenance fee).

Today, however, most public research institutions have overcome their reluctance to apply for patent protection. Some universities even derive considerable royalty revenue from biomedical inventions that they license to the private sector.[33] The Bayh-Dole Act encourages these collaborations between the public and the private sector.[34] Therefore, the need for marketing exclusivity as an alternative to patent protection is now considerably limited.

c. *Unpatentable Categories of Pharmaceutical Inventions?*

Congress introduced marketing exclusivity with the primary objective of encouraging "the development and testing of unpatentable pharmaceuticals."[35] Implicitly, it assumed that some drugs could not, for some reasons, satisfy the requirements for a patent. This begs the question whether this is still the case today.

Biopharmaceuticals[36] have been said to have a greater need for marketing exclusivity because they could not be patented.[37] In recent years however, patent offices—both

[30] *See generally* 35 U.S.C. § 112.

[31] *See infra* subpt. III.A.4.

[32] *See Health Registration Data Exclusivity, Biomedical Research, and Restrictions on the Introduction of Generic Drugs, Before the Subcomm. on Labor, Health and Human Services and Education and Related Agencies of the Senate Comm. on Appropriations* (Oct. 21, 1997) (statement of James P. Love), *at* http://www.cptech.org/pharm/senhregd.html (last visited Feb. 15, 2005) [hereinafter Love Statement, Data Exclusivity].

[33] *See* U.S. PATENT AND TRADEMARK OFFICE (USPTO), U.S. COLLEGES AND UNIVERSITIES—UTILITY PATENT GRANTS, CALENDAR YEARS 1969-2000, *at* http://www.uspto.gov/web/offices/ac/ido/oeip/taf/univ/univ_toc.htm (last visited Feb. 15, 2005); Association of University Technology Managers (AUTM), AUTM Summary Licensing Survey FY 2002, *at* http://www.ipal.de/cmsupload/2002%20Licensing%20Survey%20Summary.pdf (last visited Feb. 24, 2005).

[34] *See* The Patent and Trademark Law Amendments Act, Pub. L. No. 96-517 (1980), and its amendments, Pub. L. No. 98-620 (1984) (codified at 35 U.S.C. §§ 200-212).

[35] *See* Allergan v. Alcon, 324 F.3d 1322, 1325 (Fed. Cir. 2003), *cert. denied,* (citing H.R. REP. NO. 98-857, pt.1, at 29 (1984), *reprinted in* 1984 U.S.C.C.A.N. 2647, 2647-48), *at* http://www.ll.georgetown.edu/federal/judicial/fed/opinions/02opinions/02-1449.html (last visited Feb. 15, 2005).

[36] For a definition of biologics (biopharmaceuticals), see, e.g., PHRMA, ISSUES AND QUESTIONS ON BIOLOGICS—CAN THERE BE ABBREVIATED APPLICATIONS, "GENERICS" OR "FOLLOW-ON" PRODUCTS? 1-2, (Oct. 11, 2001), *at* http://www.europabio.org/documents/QA-Pharma.doc (last visited Feb. 24, 2005).

[37] According to EGA, marketing/data exclusivity

> was created at a time when there were no patents for biotech products. This data exclusivity period therefore provided a form of market protection for these products in the absence of patents, which was particularly important to those Member States with developing biotech industries. Patents now exist for biotech products.

EGA, MAJOR OBSTACLE, *supra* note 22, at 4. *See also* Richard F. Kingham & Grant H. Castle, *Data and Marketing Exclusivity for Pharmaceuticals in the European Community*, 55 FOOD & DRUG L.J 209 (2000).

the U.S. Patent and Trademark Office (PTO)[38] and the European Patent Office (EPO)[39]—have adapted their rules and practices to facilitate the patenting of biotechnological inventions. Therefore, biopharmaceuticals and "ordinary" pharmaceuticals currently receive approximately equivalent patent protection.[40]

A similar argument was made for research into new uses (i.e., therapeutic indications) of "old" compounds.[41] In the past, new uses were not always eligible for patent protection. Today however, they are eligible for twenty-year patents. Admittedly, this protection is not optimal because physicians are free to prescribe "off-label" the generic version of the old compound.[42] As discussed *infra* in subpart III.C.5., marketing exclusivity however does not close this loophole.

2. *To Induce the Generation of Preclinical and Clinical Data*

The research-based pharmaceutical industry has claimed that marketing exclusivity provides "the necessary incentives for companies to generate the necessary data that accompanies registrational packages for medicinal products."[43] It implies that, without marketing exclusivity, brand-name companies would not want to conduct (very expensive) preclinical tests and clinical trials.

Such a line of argument has to be rejected. Pharmaceutical companies do not need incentives to produce preclinical and clinical test data because they have no choice in that matter: they must supply this information if they want to sell their drugs. Preclinical testing and clinical trials are a requisite for any new drug marketing application. These tests have to be supplied to the drug agency, whether or not marketing exclusivity is granted. Marketing exclusivity is not designed to encourage firms to provide better-designed clinical trials or more comprehensive preclinical tests; the nature and extent of the tests and trials are essentially dictated by the drug agency.

3. *To Limit Proprietary Interests*

The research-based pharmaceutical industry has tried to argue that marketing exclusivity rules are intended to limit the duration of the exclusive use of data, which, absent such regulations, would last indefinitely. According to the International Federation of Pharmaceutical Manufacturers Associations (IFPMA), "[a]rguably, if a country had no data protection law at all, then the data submitted as part of a registrational package should never be permitted to be referred to by a generic company."[44]

This argument is misleading, if not deceptive. The default rule is not a blanket prohibition against reliance by the second entrant on the application file provided to the drug

[38] *See* USPTO, Revised Interim Utility Guidelines Training Materials (2000), *at* http://www.uspto.gov/web/menu/utility.pdf (last visited Feb. 15, 2005).

[39] *See* Rules 23b to 23e, and 27a to 28a to the European Patent Convention, *at* http://www.european-patent-office.org/legal/epc/e/ma2.html#REG (last visited Feb. 15, 2005); European Patent Office (EPO), Guidelines for Examination in the European Patent Office, Chaps A.IV.4., A.IV.5. C.II.6, C.IV.2a (Oct. 2001), *at* http://www.european-patent-office.org/legal/gui_lines/pdf/gui_e_full.pdf (last visited Feb. 15, 2005).

[40] In addition, as of this writing, there is no well-established route to develop a generic of a biological drug, whereas generic manufacturers of "ordinary" pharmaceuticals can file straightforward abridged/abbreviated applications.

[41] *See* Kingham & Castle, *supra* note 37, at 223.

[42] Off-label practices allow physicians to prescribe the generic drug for the new—and patented—use even though this therapeutic indication is not on the generic drug's approved labeling. *See also Organon v. Teva Pharm.*, 244 F. Supp. 2d at 370.

[43] *See* IFPMA, ENCOURAGEMENT, *supra* note 6, at 1.

[44] *Id.* at 2.

agency by the pioneer company. On the contrary, absent regulations on the subject, a country could decide that marketing applications are fully available to the public, including generic competitors.[45] Once a pioneer company decides to supply its preclinical and clinical data to a drug agency, it loses the right to control further release of this information, unless a regulation or an administrative practice grants such a right.

There are valid public policy reasons for limiting the duration of marketing exclusivity. Foremost is the concern that animals are sacrificed unnecessarily and research subjects dangerously exploited if the second applicant has to replicate studies already performed by the pioneer company. If the second applicant has to repeat the entire program of preclinical safety studies, it will have to use and kill dozens, if not hundreds, of laboratory animals; similarly, if it must conduct the full range of clinical trials, thousands of subjects will need to be enrolled in studies that will not elicit any new knowledge. This lack of scientific rationale makes such studies unethical. In the words of FDA, "it is wasteful and unnecessary to carry out studies to demonstrate what is already known about a drug."[46] It is therefore reasonable to exempt—at some point in time—second entrants from the typical testing requirements that are imposed on the first entrant.

B. *Practical Significance of Marketing Exclusivity*

News reports regularly draw attention to the high number of patents covering drugs. According to these media stories,[47] generic competition is stifled because brand-name companies keep piling up new patents. Furthermore, the inventions covered by these patents are of limited intrinsic value. For instance, companies have started to patent the metabolites of their already-patented drugs;[48] others have patented specific drug dosage forms.[49] The impression left by these accounts is that patents are so easy to obtain that marketing exclusivity is not necessary to promote drug R&D. If a firm can get not one, but several, twenty-year patents for all aspects of its drug, without—at least in practice—being unduly encumbered by the nonobviousness requirement,[50] nonpatent exclusivities are unnecessary.

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[45] While Article 39.3 of the Trade-Related Aspects of Intellectual Property Rights Agreement (TRIPS) does require World Trade Organization (WTO) countries to adopt some form of data protection, it is not self-executing and its exact scope is the subject of controversy. *See also* CARLOS MARIA CORREA, PROTECTION OF DATA SUBMITTED FOR THE REGISTRATION OF PHARMACEUTICALS: IMPLEMENTING THE STANDARDS OF THE TRIPS AGREEMENT (South Centre 2002), *at* http://www.southcentre.org/publications/protection/protection.pdf (last visited Feb. 15, 2005). *See generally* IFPMA, A REVIEW OF EXISTING DATA EXCLUSIVITY LEGISLATION IN SELECTED COUNTRIES (3d ed. 2004), *at* http://www.ifpma.org/documents/NR356/DE_01_16_2004_2.doc (last visited Feb. 15, 2005).

[46] *See* FDA, 505(b)(2) Draft Guidance, *supra* note 3, at 3.

[47] *See, e.g.*, Gardiner Harris, *Bristol-Myers Set to Settle BuSpar Generics Lawsuit*, WALL ST. J., Jan. 7, 2003, at D3.

[48] *See, e.g.,* Letter from Gary L. Yingling, McKenna & Cuneo, L.L.P. to Cecelia Parise, Office of Generic Drugs, FDA (Feb. 15, 2000), *at* http://www.fda.gov/ohrms/dockets/dailys/00/mar00/031500/c000070.pdf (last visited Feb. 15, 2005); Robert Langreth & Victoria Murphy, *Perennial Patents*, FORBES, Apr. 2, 2001, *at* http://www.spancoalition.org/News/news4.2.01.htm (last visited Feb. 15, 2005); FTC, Complaint against Bristol Myers Squibb Corporation (2003), *at* http://www.ftc.gov/os/2003/03/bristolmyerscmp.pdf (last visited Feb. 15, 2005); Peter O. Safir, *Current Issues in the Pioneer Versus Generic Drug Wars*, 50 FOOD & DRUG L.J. 335, 337 (1995).

[49] *See, e.g.,* Astra Aktiebolag v. Andrx Pharms., Inc., 222 F. Supp. 2d 423 (D.C. N.Y. 2002).

[50] Even if the patent is not strong and even if it is ultimately found invalid, the rules applied by FDA in connection with *Orange Book* listing of patents gives an automatic advantage to the patent holder: the marketing application of a generic competitor will be stayed (i.e., delayed) for several months. *See also* note 57, *infra*.

To check this hypothesis, this subpart reviews U.S. patents and exclusivities listed in FDA's *Orange Book*[51] for a set of new prescription (Rx) drugs approved between 1998 and February 2004.[52] The purpose of this analysis is to assess whether exclusivity protections ever outlast or "replace" patent protections.

During the time period under consideration, FDA approved 137 drugs. Their periods of patent protection and of exclusivity were calculated and compared; for twenty-three drugs out of this 137 total, the period of marketing exclusivity extended past the expiry of the last patent.[53] Twenty-two drugs (among those twenty-three) had no patent listed in the *Orange Book*. Three additional drugs (not counted among the twenty-three) had orphan drug exclusivity[54] running longer than patents.[55] One additional drug was protected neither by patent nor by exclusivity.[56] In summary, out of 137 drugs, twenty-seven were developed without "substantial" patent protection.

This analysis is subject to several limitations. First, recently-issued and to-be-issued patents are not yet listed in the *Orange Book*. Pharmaceutical companies tend to list new patents in the *Orange Book* just before their previously-listed patents are to expire.[57] Several drugs had requests for patent term extension/restoration pending.[58] Simi-

[51] The *Orange Book* is the common name for FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* publication. The *Orange Book* can be consulted online at http://www.fda.gov/cder/ob/default.htm (last visited Feb. 15, 2005). Because the European authority does not provide the same convenient search tool, the exercise could not be repeated for the European Union. *See also* Kingham & Castle, *supra* note 37, at 218, 223.

[52] Only drugs listed by FDA on its web page as of February 28, 2004 (*at* http://www.fda.gov/cder/consumerinfo/default.htm) were taken into consideration for analysis. This web page does not immediately list all newly-approved drugs. No data could be obtained for one drug (Raptiva) among the set of 137 drugs. The *Orange Book* analysis was performed in March 2004. Because information in the *Orange Book* is often updated, the same analysis could yield different results today.

[53] A summary of the results of this analysis are available at http://www.pharmalaw.org/marketing%20exclusivity%20dates%20(12.3.04).doc (last visited Feb. 24, 2005).

[54] The Orphan Drug Act, Pub. L. No. 97-414 (codified at 21 U.S.C. § 360aa) is available at http://www.fda.gov/orphan/oda.htm (last visited Feb. 15, 2005). FDA regulations in 21 C.F.R. § 316 are available at http://www.access.gpo.gov/nara/cfr/waisidx_02/21cfr316_02.html (last visited Feb. 15, 2005).

[55] The drugs are:

Aromasin (Pharmacia) has an orphan drug exclusivity period that exceeds its patent period; *at* http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexclnew.cfm?Appl_No=020753&Product_No=001&table1=OB_Rx (last visited Feb. 24, 2005).

Ellence (Pharmacia & Upjohn) is covered only by orphan drug exclusivity; *at* http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexclnew.cfm?Appl_No=050778&Product_No=001&table1=OB_Rx (last visited Feb.24, 2005).

Zometa has longer orphan drug protection than patent protection; *at* http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexclnew.cfm?Appl_No=021223&Product_No=001&table1=OB_Rx (last visited Feb. 24, 2005).

[56] Synercid is wholly unprotected, *at* http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?Appl_No=050748&TABLE1=OB_Rx (last visited Feb. 25, 2005).

[57] This practice is particularly objectionable when a brand-name company lists a new patent after a generic competitor has filed its application to copy the innovator product. In the past, such a practice resulted in several additional 30-month stays (of generic competition) as per the Hatch-Waxman Act. *See further* Aidan Hollis, *Closing the FDA's Orange Book*, 24 (4) REG. MAG. 14-17 (Winter 2001), *at* http://www.cato.org/pubs/regulation/regv24n4/v24n4-2.pdf (last visited Feb. 15, 2005).

The Act has now been modified to allow only one 30-month stay. *See* Medicare Prescription Drug, Improvement and Modernization Act of 2003, Pub. L. No. 108-173, Title XI, § 1101, *at* http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=108_cong_bills&docid=f:h1enr.txt.pdf (last visited Feb. 15, 2005).

[58] Pharmaceutical companies can apply for patent restoration/extension based on the length of clinical development and of the FDA registration procedure. *See* FDA, Frequently Asked Questions on the Patent Term Restoration Program (last updated Dec. 8, 2003), *at* http://www.fda.gov/cder/about/smallbiz/patent_term.htm (last visited Feb. 15, 2005). *See also* Karin L. Tyson, *The Role of Patent and Trademark Office Under 35 U.S.C. Section 156*, 54 FOOD & DRUG L.J. 205 (1999).

larly, the *Orange Book* lists only current marketing exclusivities. When a patent is about to expire, a pharmaceutical company also may decide to seek a new marketing exclusivity. For instance, it may introduce a new indication for its existing drug, which will make the latter eligible for a three-year marketing exclusivity (*see infra* Part III.A.2.). Thus, when patents are nearing their expiration dates, marketing exclusivity gains additional practical importance. Because the studied set of drugs consists only of recently-approved products, it may not fully reflect the significance of patent and marketing exclusivity throughout the product's life cycle. Finally, certain patents (e.g., process patents[59]) are not eligible for listing in the *Orange Book*.[60]

Despite these limitations, this analysis shows that marketing exclusivity does confer protection in a modest proportion of new drugs. This, by itself, does not prove conclusively that these twenty-three drugs would *not* have been developed had it not been for marketing exclusivity. Nevertheless, thanks to their marketing exclusivity, these twenty-three drugs are (or were) temporarily sheltered from generic competition.[61]

III. MARKETING EXCLUSIVITY IN THE UNITED STATES

A. *General Considerations*

1. *Definition*

Nonpatent exclusivities for brand-name drug companies originate from three sources:[62] 1) Hatch-Waxman or new drug product exclusivity;[63] 2) orphan drug exclusivity;[64] and 3)

[59] While process patents cannot be listed in the *Orange Book,* formulation patents can be. *See* Terry G. Mahn, *Patenting Drug Products: Anticipating Hatch-Waxman Issues During the Claims Drafting Process*, 54 FOOD & DRUG L.J. 245, 251-52 (1999). Formulation patents seem to play a role analogous to process patents. Like process patents, they are weaker than product patents. Hence, generic competitors often are able to design around formulation patents. *See* Elizabeth H. Dickinson, *FDA's Role in Making Exclusivity Determinations*, 54 FOOD & DRUG L.J. 195, 197 (1999).

[60] According to 21 U.S.C. § 355(b)(1),

> [t]he applicant shall file with the application the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug and with respect to which a claim of patent infringement could *reasonably be asserted* if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug.

See also the FTC's report, which surveys the rules regarding patents that can be listed in the *Orange Book.* FTC, GENERIC DRUG ENTRY PRIOR TO PATENT EXPIRATION: AN FTC STUDY (July 2000), *at* http://www.ftc.gov/os/2002/07/genericdrugstudy.pdf (last visited Feb. 15, 2005). *See also* InsideHealthPolicy.com*,* Can Patents Not Claiming Substance in Approved Drug Be Listed? GPhA, PhRMA Clash on Listing of Some Drug Substance Patents (Jan. 6, 2003), *at* http://lists.essential.org/pipermail/ip-health/2003-January/004018.html (last visited Feb. 15, 2005).

[61] As explained in subpart III.A.4., it is quite difficult for a generic competitor to attack a marketing exclusivity.

[62] Generic companies may benefit from a 180-day exclusivity when they attack a brand-name company's patent (the so-called paragraph IV certification); this article does not delve into this subject.

[63] The Hatch-Waxman amendments were enacted as the Drug Price Competition and Patent Term Restoration of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (1984) (codified at 21 U.S.C. §§ 301-392). Engelberg explains that the grant of marketing exclusivities was key in convincing PhRMA (then named PMA) and its members to accept the 1984 Hatch-Waxman Amendments and, in particular, its *Bolar* exemption. "Beyond question, the five-year non-patent exclusivity … was the key to the compromise." Engelberg, *supra* note 16, at 406 (reviewing the genesis of the bill and providing a detailed account of the negotiations between innovator and generic industry groups that ultimately led to the enactment of the Act).

[64] Orphan drug exclusivities are governed by 21 U.S.C. § 360cc and 21 C.F.R. pt. 316, *available from* http://www.access.gpo.gov/nara/cfr/waisidx_99/21cfr316_99.html (last visited Feb. 15, 2005). *See also* FDA, The Orphan Drug Regulations (Final Rule), 57 Fed. Reg. 62,076 (Dec. 29, 1992), *at* http://www.fda.gov/orphan/odreg.htm (last visited Feb. 15, 2005); Gary A. Pulsinelli, *The Orphan Drug Act: What's Right With It?*, 15 COMPUTER & HIGH TECH. L.J. 299 (1999).

pediatric exclusivity.[65] As already mentioned, this paper focuses only on the first category, and its scope is limited to drugs.[66] Disregarding marketing exclusivity conceded to drugs approved by FDA between 1982 and 1984,[67] there are two main categories of marketing exclusivity:

- the five-year marketing exclusivity for new chemical entities (NCEs), and
- the three-year marketing exclusivity for non-NCE drugs for which new clinical investigations were submitted.

These two types of exclusivity often are combined. A new drug starts with the five-year exclusivity; at some point in time, generally before its patent and/or its five-year exclusivity expires, the drug sponsor performs clinical trials qualifying the drug[68] for an additional three-year exclusivity. Similarly, three-year periods of exclusivity can be added up, preferably for the innovator company, in a sequential fashion so that the total period of exclusivity is stretched to its maximum.

FDA determines autonomously whether the conditions for marketing exclusivity are met. The applicant must indicate whether it is claiming any exclusivity.[69] Even if the latter fails to do so, however, FDA will reach its own decision and grant exclusivity as long as the material requirements are fulfilled.[70] The agency has no formal process to inform the applicant that it was granted a marketing exclusivity, but this information is available immediately in the *Orange Book*.[71]

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[65] In the United States, pediatric exclusivities are governed by 21 U.S.C. § 355a (FDCA § 505A). *See also* CDER, FDA, Guidance for Industry: Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act (Sept. 1999), *at* http://www.fda.gov/cber/gdlns/pedexc.pdf (last visited Feb. 15, 2005); Kurt R. Karst, *Pediatric Testing of Prescription Drugs: The Food and Drug Administration's Carrot and Stick for the Pharmaceutical Industry*, 49 AM. U. L. REV. 739 (2000). The European Union is contemplating the addition of a marketing exclusivity period to encourage clinical studies in pediatric populations; it plans to emulate closely the U.S. system. *See* European Commission, Better Medicines for Children, Consultation Document (Feb. 28, 2002, *at* http://pharmacos.eudra.org/F2/pharmacos/docs/Doc2002/feb/cd_pediatrics_en.pdf (last visited Feb. 15, 2005); European Commission, Regulation on Medicines for Children: Frequently Asked Questions (Sept. 2004), *at* http://pharmacos.eudra.org/F2/Paediatrics/docs/Paeds%20Q&A%20October%2028.pdf (last visited Feb. 24, 2005).

[66] Exclusivity for medical devices is governed by a different set of rules. *See* Center for Devices and Radiological Health (CDRH), FDA, Guidance for Industry and for FDA Reviewers on Section 216 of the Food and Drug Administration Modernization Act of 1997 (FDAMA) (Aug. 9, 2000), *at* www.fda.gov/cdrh/ode/guidance/1135.html (last visited Feb. 15, 2005). FDAMA § 216 establishes a six-year rule of marketing exclusivity for certain medical devices.

[67] Because this class of marketing exclusivity is no longer granted, it is not analyzed here. *See* 35 U.S.C. § 355(j)(4)(D)(i), (c)(3)(D)(i).

[68] More accurately, it is not the drug in its entirety that is protected by the additional exclusivity, but only the changes that FDA approved on the basis of the new clinical trial. As explained in subpart III.C.5. *infra*, once the initial period of exclusivity has expired, the drug (as covered by this exclusivity) becomes an admissible target for generic competition; only the *new* aspects covered by the subsequent (and still current) exclusivities remain sheltered from generic competition.

[69] FDA requires that the applicant provide a detailed explanation as to the basis of its exclusivity. 21.C.F.R. §§ 314.50(j), 314.54(a)(1)(vii), and 314.70(f). *See also* FDA, Abbreviated New Drug Application Regulations, Patent and Exclusivity Provisions (Final Rule), 59 Fed. Reg. 50,338, at III.D and III.E (Oct. 3, 1994) [hereinafter FDA, 1994 ANDA Final Rule].

[70] According to FDA's Frequently Asked Questions (FAQs) on exclusivity, "[t]here is no requirement to apply . . . . There is a procedure in CDER that provides review of all relevant applications, with or without a request from the applicant, for an exclusivity determination." CDER, FDA, Frequently Asked Questions for New Drug Product Exclusivity, question 16 (Aug. 30, 2001), *at* http://www.fda.gov/cder/about/smallbiz/exclusivity.htm (last visited Feb. 15, 2005) [hereinafter FDA, FAQs on Exclusivity].

[71] *See* CDER, FDA, Frequently Asked Questions on Patents and Exclusivity (last updated Mar. 8, 2001), *at* http://www.fda.gov/cder/ob/faqs.htm (last visited Feb. 15, 2005).

2. *The Notion of Reliance*

Marketing exclusivity precludes a second applicant from relying on the data previously provided to demonstrate the safety and efficacy of the reference drug.[72] In the United States, reliance is understood broadly as direct or indirect "use" of the pioneer's clinical or preclinical data (supporting safety and/or efficacy of the drug). In practice, the second entrant does not directly see, nor use the pioneer's data. Its reliance is only indirect: it is exempted from having to prove safety and efficacy because FDA is aware that the pioneer company already has demonstrated safety and efficacy.[73] Reliance is present even if FDA did not have to open—and *a fortiori* study—the reference drug's marketing application file in order to approve the second entrant's application.[74]

In contrast, other countries have proposed different interpretations of the reliance notion. In Canada, for example, cases where the second applicant is said to rely on the pioneer's data are infrequent because if the Canadian drug agency finds it possible to approve the generic application only on the basis of the information contained therein, there is held to be no reliance.[75] More precisely, the implicit guarantee of safety and efficacy that the agency has obtained through its experience with the reference drug is not enough to constitute "reliance." Other countries allow a generic to be marketed simply if the same product has been authorized abroad, thus forestalling the need for reliance.[76]

Even in the United States, there is no reliance if the second applicant only refers to general knowledge that is restated in the pioneer company's application. Moreover, second applicants can freely refer to published information. For example, they can introduce publicly-available evidence about "disease etiology, support for particular endpoints, [and] methods of analysis."[77] If the pioneer company published its clinical

[72] The data submitted by the pioneer and relied upon by the second entrant must have been *reviewed and accepted* by FDA. "Therefore, if a sponsor has submitted a study to an NDA, the results of which are not reflected in the NDA's approval (e.g., a study for an indication that FDA has rejected), a 505(b)(2) applicant cannot rely on that study to support its own approval." Letter from Steven K. Galson, M.D., M.P.H., Acting Director, CDER, FDA's to Messrs. Donald O. Beers, Arnold & Porter L.L.P. and William F. Cavanaugh, Jr., Patterson, Belknap, Webb & Tyler L.L.P., in response to their citizen petition on behalf of Abbott (Nov.30, 2004), at 8, *at* http://www.fda.gov/ohrms/dockets/dockets/04p0386/04p-0386-pdn00001-vol1.pdf (last visited Feb. 24, 2005).

[73] Ian Dodds-Smith writes that the authority has "the comfort of knowing that the full data" submitted by the first applicant establishes safety and efficacy. *See* Ian Dodds-Smith, *Data Protection and Abridged Applications for Marketing Authorisations in the Pharmaceutical Industry*, *in* PHARMACEUTICAL MEDICINE, BIOTECHNOLOGY AND EUROPEAN LAW 96 (Richard Goldberg & Julian Lonbay ed., Cambridge Univ. Press 2000). *See also* EGA, Data Exclusivity and Market Protection (2004), *at* http://egagenerics.com/gen-dataex.htm (last visited February 24, 2005).

[74] "Under the new Act, FDA reviewers do not actually review the pioneer drug data, but merely review certain product-specified descriptions of the generic product." James T. O'Reilly, *Knowledge Is Power: Legislative Control of Drug Industry Trade Secrets*, 54 U. CIN. L. REV. 1, 22, n.124 (1985).

[75] According to the Federal Court of Canada,

> C.08.004.1 [i.e., the provision conferring a five-year exclusivity] was not intended to create a protection analogous to a patent for the benefit of the innovators. The Minister does not "rely" on the innovator's information for the purpose of C.08.004.1 when considering an ANDS for a NOC [Notice of Compliance] when the Minister issues the NOC solely on the basis of information contained in the ANDS. Given the overall purpose of the Regulations, the adverb 'indirectly' should not be read into C.08.004.1(1) so as to broaden the scope of the verb 'relies.'

Bayer, Inc. v. Canada (Attorney General), 1. F.C. 553, 556 (1998). This judgment was appealed and confirmed by the Canadian Federal Court of Appeal, 87 C.P.R. (3d) 293 (1999). *See also* Edward Hore, *A Comparison of United States and Canadian Laws as They Affect Generic Pharmaceutical Market Entry*, 55 FOOD & DRUG L.J. 373, 387 (2000).

[76] *See* IFPMA, ENCOURAGEMENT, *supra* note 6, at 9-10.

[77] *See* FDA, 505(b)(2) Draft Guidance, *supra* note 3, at 2.

trial findings and made its raw data available to the public (admittedly a rare occurrence), second entrants can refer to this information without being deemed to rely on the pioneer application.[78]

Reliance can extend to original data submitted in support of a discontinued reference drug. For the second entrant's application to be approved, however, the withdrawal of the pioneer drug must not be attributable to safety or efficacy concerns.[79] When, on the other hand, the reference product was discontinued for another reason (e.g., because its sponsors choose to introduce a newer version of the drug), the second applicant's reliance on the "old" drug's data entails no health risk and is permissible. Even for FDA, determining the exact reason for withdrawal can be a difficult endeavor; [80] the pioneer firm's own assessment is not decisive.[81]

3. *Avoiding the Marketing Exclusivity Bar*

There are three situations where marketing exclusivity does not block the second applicant's entry on the market. First, as alluded to before, the second applicant that generates and submits its own data establishing the safety and efficacy of its drug[82] is entitled to receive marketing approval even if the pioneer drug's period of exclusivity is still running.[83] In that case, the second entrant submits a so-called full or "stand-alone" application under section 505(b)(1).[84] In practice however, repeating the pioneer's clinical trials is extremely difficult, costly, and burdensome.[85] Therefore, generic companies usually avoid the 505(b)(1) route. It is worth noting that a second entrant's effort to generate its own data does not open the gate for a third entrant, because the agency has decided that a third entrant cannot rely on the second applicant's data, even though these are not protected.[86] According to FDA, allowing

[78] *See id*. at 12.

[79] *See* CDER, FDA, Referencing Discontinued Labeling for Listed Drugs in Abbreviated New Drug Applications, Availability (draft guidance) (Oct. 26, 2000), 65 Fed. Reg. 64,225, *at* http://www.fda.gov/cder/guidance/3660dft.pdf (last visited Feb. 15, 2005) [hereinafter FDA, Discontinued Draft Guidance].

[80] FDA publishes in the *Federal Register* its determination to maintain a discontinued drug as a reference listed drug in the *Orange Book*. *See* 21 C.F.R. §314.162. *See, e.g.*, FDA response to Mr. Simmons' citizen petition (Jan. 27, 2003), *at* http://www.fda.gov/ohrms/dockets/dailys/03/Feb03/020303/8004ca9b.pdf (last visited Feb. 24, 2005).

[81] See the detailed analysis performed by the FDA in its letter answering the citizen petition filed by Mr. Mahn (counsel for Allergan), (May 21, 2003), at 3-11, *at* http://www.fda.gov/ohrms/dockets/dailys/03/May03/052903/02p-0469-pdn0001-vol1.pdf (last visited Feb. 24, 2005).

[82] Efficacy "is used to denote the use and evaluation of a health care technology under highly controlled conditions by unusually qualified practitioners." Effectiveness refers to benefits of a treatment under normal conditions of use (e.g., under the care of a medical doctor). Institute of Medicine, Food and Drug Administration Advisory Committees 1992, *at* http://print.nap.edu/pdf/0309048370/pdf_image/224.pdf (last visited Feb. 15, 2005).

[83] *See* Burroughs Wellcome v. Bowen, 630 F. Supp. 787 (N.C. 1986). Obviously, there should not be any valid patent or any other exclusivity protecting the innovator's drug. Both ANDA and 505(b)(2) must certify to any patents covering the pioneer company's reference listed drug. *See, e.g.*, FDA's letter to Messrs. Beers and Cavanaugh, *supra* note 72.

[84] *See, e.g.,* FDA, 1994 ANDA Final Rule, *supra* note 69, at III.J; FDA letter to Messrs. Allera and Segal (Feb. 16, 2000) in response to their petition, *at* http://www.fda.gov/ohrms/dockets/dailys/00/mar00/030200/pdn0001.pdf (last visited Feb. 24, 2005).

[85] If the generic firm nevertheless succeeds in carrying out the appropriate trials, its effort normally will not be rewarded by a marketing exclusivity because the firm is simply replicating existing studies and is not introducing an NCE (but merely a copy of an already-approved NCE).

[86] For example, if company A has a five-year exclusivity and company B generates its own safety and efficacy data and obtains marketing approval before the expiry of company A's five-year exclusivity period, company C will not be allowed to rely on company B's data even though company B's data are not protected by an exclusivity period. In other words, company C is prevented from relying on company B's data because of the far-reaching effects of company A's exclusivity. FDA acknowledged that the statute was ambiguous in that respect, but chose to privilege the pioneer drug company by maintaining its R&D incentive to the greatest extent. *See* FDA, Abbreviated New Drug Application Regulations, Proposed Rule, 54 Fed. Reg. 28,872, at L.1 (July 10, 1989) [hereinafter FDA, Proposed ANDA Rule].

such reliance would deprive the pioneer company of an effective period of marketing exclusivity.[87]

The second exception pertains to applicants that have obtained a "right of reference" from the pioneer firm.[88] This right of reference consists of the permission given by the pioneer company to rely on its data; the beneficiary of this right can submit its application regardless of marketing exclusivity.[89] FDA asks to see written confirmation of this permission.[90] Agreements conceding rights of reference are uncommon; brand-name companies usually have no reason to give such consent, even against financial consideration.[91] Therefore, it is assumed throughout this paper that the second applicant does *not* have a right of reference.

4. *Challenging Marketing Exclusivity?*

Marketing exclusivity confers a very strong protection to the pioneer company because competitors cannot really challenge it.[92] Once FDA has decided that exclusivity is warranted, a rival firm can first ask for reconsideration;[93] if FDA maintains its position, the interested party must then petition FDA.[94] There is no procedure akin to that applying to invalid or "not-infringed" patents (i.e., the paragraph IV certification).

So far, there has been no sanction imposed for improperly obtained exclusivities. This may occur in the future, given that the Federal Trade Commission (FTC) has sued drug companies that improperly list patents in the *Orange Book*.[95] The FTC con-

[87] A good argument in favor of this interpretation is that if reliance on a second set of data were allowed, the pioneer firm would be severely restricted in its ability to license the drug.

> For the same reasons, an innovator whose drug was entitled to exclusivity could not license another company to make a copy of the pioneer drug without losing the value of its exclusivity. Under the narrow theory of exclusivity, once the licensed company's product was approved, ANDA applicants could copy the licensed product, without regard to the innovator's exclusivity.

FDA, Proposed ANDA Rule, *supra* note 86.

[88] The beneficiary of a marketing exclusivity can also waive it. *See, e.g.*, FDA response to citizen petition by Messrs. Rein and McGrath (on behalf of Pfizer) (Jul. 2, 2004), at 9-11, *at* http://www.fda.gov/ohrms/dockets/dailys/04/july04/070704/04p-0227-pdn0001.pdf (last visited Feb. 24, 2005).

[89] This application is categorized as a 505(b)(1) application if it relies only on the applicant's own studies and/or on information for which it obtained a right of reference. *See* FDA, 505(b)(2) Draft Guidance, *supra* note 3, at 2-3.

[90] 21 C.F.R. § 314.50(g)(3).

[91] Brand-name companies will not risk losing market share to lower-priced copies. Especially for high-sale drugs, market shares translate into high value so that a generic manufacturer is not in a position to offer a payment that would fully compensate the loss incurred by the brand-name firm. The expected profits of the generic firm are lower than the expected loss of the originator firm, because the generic firm sells its product at a lower price than the originator firm. The difference between the one firm's profit and the other's loss is what the public gains through lower prices.

[92] The other side of the coin is that, once FDA has refused exclusivity, it is very hard for the innovator company to challenge this rejection; courts give great deference to scientific decisions reached by FDA. In the case of *Upjohn v. Kessler*, the court found that, when the agency had not specifically required a clinical trial (in that case to support an Rx-to-OTC switch), it could refuse exclusivity on the basis that the submitted study was not essential; the court would not challenge such an FDA finding as long as the agency "considered the statutory factors governing exclusivity, considered the relevant data, and arrived at a rational decision based on the evidence." 938 F. Supp. 439, 445 (D. Mich. 1996).

[93] *See* FDA, Proposed ANDA Rule, *supra* note 86, at section L.3; FDA, 1994 ANDA Final Rule, *supra* note 69, at III.J., cmt. 95 (mentioning that interested parties can file citizen petitions to oppose a marketing exclusivity grant). *See also* Abbott v. Young, 920 F.2d 984 (Fed. Cir. 1990) (in which a drug sponsor filed a citizen petition attacking the length of marketing exclusivity granted by FDA).

[94] *See* 21 C.F.R. § 10.25(a).

[95] *See, e.g.,* Press Release, FTC, Wrongful "Orange Book" Listing Raises Red Flag With FTC; Leads to Consent Order With Biovail Corp. Concerning Its Drug Tiazac (Apr. 23, 2002), *at* http://www.ftc.gov/opa/2002/04/biovailtiazac.htm (last visited Feb. 15, 2005). Improperly obtained marketing exclusivities are certainly less likely than improperly listed patents.

demns such practice for the anticompetitive harm it causes by unduly blocking generic entry.

Contrary to orphan drug exclusivity, Hatch-Waxman marketing exclusivity is not lifted if the second applicant's drug is proved clinically superior to the pioneer/reference drug.[96]

Marketing exclusivity also differs from a patent in that it is not a right that the pioneer firm (i.e., the first entrant) can invoke directly against the second entrant. In particular, the pioneer firm cannot directly challenge the second entrant to whom the agency would have mistakenly granted marketing approval, despite an ongoing marketing exclusivity. In such a hypothesis, the pioneer company must complain to (or sue) FDA. Such a lawsuit is not ripe, however, if the agency decides to classify a competitor's marketing application as a full 505(b)(1) NDA, whereas the pioneer firm would argue that the rival application should be treated as an—exclusivity-barred—generic or 505(b)(2) application.[97] Only after FDA reaches its final decision on marketing approval of the second entrant's 505(b)(1) application, is the lawsuit by the pioneer company deemed ripe.[98]

B. *The Five-Year Marketing Exclusivity*

1. *Legal Basis and Effects*

The statutory basis for the five-year exclusivity is found in 21 U.S.C. §§ 355(c)(3)(D)(ii) and 355(j)(5)(D)(ii).[99] Exclusivity starts running with FDA approval of the reference drug's new drug application (NDA).[100] For five years from this date, FDA cannot even accept a second entrant's application that "relies" on the data submitted in support of this NDA.[101] Because FDA takes an average of eighteen months to approve a generic application,[102] the five-year marketing exclusivity delays competition by about 6.5 years following the date of the reference drug's approval.[103] Because the exclusivity begins only with the

[96] Regarding orphan drug exclusivities, see Pulsinelli, *supra* note 64, at 314.

[97] Regarding section 505(b)(2) applications, see *supra* note 3.

[98] *See* R&D Labs., Inc. v. FDA, 2000 U.S. Dist. LEXIS 20209 (D.D.C. 2000). According to the district court, "[the statute] does not, as Plaintiff seeks, provide a right against the FDA from reviewing as a (b)(1), an application that may later fall short of (b)(1) approval, yet appear complete as a (b)(2)." *Id*. at 11.

[99] These provisions of 21 U.S.C., *at* http://www4.law.cornell.edu/uscode/21/355.html (last visited Feb. 15, 2005), correspond to FDCA §§ 505(c)(3)(D)(ii), 505(j)(4)(D)(ii), *at* http://www.fda.gov/opacom/laws/fdcact/fdcact5a.htm (last visited Feb. 15, 2005). Alfred B. Engelberg says of the 1984 Act that it was "inelegantly drafted" and is "extremely complex." *See* Engelberg, *supra* note 16, at 391-92. This certainly is true of the provisions pertaining to marketing exclusivities.

[100] "'Date of approval' refers only to a final approval and not to a tentative approval that may become effective at a later date." 21 C.F.R § 314.108(a).

[101] The ban on application acceptance encompasses all ANDAs or 505(b)(2) NDAs for drugs that contain the same active ingredient (active moiety) and that rely on the pioneer's data. Even when the subsequent application is for a different use for, or a different form of, the active ingredient (e.g., a different salt), the ban is not lifted. Dickinson, *supra* note 59, at 200.

[102] According to FDA/CDER's *Report to the Nation for 2003*,

> We approved 263 generic drug products in 2003 … . The median approval time for generic drugs was 17 months. The median statistic for total approval time has hovered at about 18 to 19 months for six years. We made changes to decrease the overall time to approval of applications by three months over the next three to five years.

CDER, FDA, REPORT TO THE NATION FOR 2003; IMPROVING PUBLIC HEALTH THROUGH HUMAN DRUGS, at 26, *available at* http://www.fda.gov/cder/reports/rtn/2003/rtn2003.pdf (last visited Feb. 15, 2005). More generally, on the approval process of ANDAs approved between 1984 and 1994, see Fiona M. Scott Morton, Who Gets Approved Quickly: Generic Drugs at the FDA (Sept. 2001), *at* http://www.som.yale.edu/Faculty/fms8/papers/fda_approvals.pdf (last visited Feb. 15, 2005).

[103] Moreover, patents on the reference drug must have expired or have been declared invalid for the second entrant to bring its rival drug on the market.

approval of the first applicant's NDA, the second applicant is not blocked if it files its 505(b)(2) NDA[104] with FDA before the agency approved the first application.[105]

The five-year period of exclusivity is reduced to four years if the second applicant challenges the validity of the pioneer drug's patent or asserts that the patent is not infringed.[106]

2. *New Chemical Entity (NCE)*

To get the five-year marketing exclusivity, only one condition must be met: the approved drug must contain a new active ingredient[107] that is an NCE or new active moiety that FDA has never approved yet.[108] Applications for NCEs usually are submitted as a 505(b)(1) NDA application. In some circumstances, however, an application for an NCE may be submitted as a 505(b)(2) application, that is an application relying in part on a third party's data.[109] The fact that the 505(b)(2) route is followed does not deprive the applicant from the five-year exclusivity reward, provided that its application was indeed for an NCE.[110]

All ester or salt forms of the compound are held to constitute one same active moiety.[111] In other words, a newly-approved drug is not eligible for a five-year exclusivity if it is simply made of a different ester form of an already-approved drug.[112] This definition of "active moiety" is important, as it demarcates five-year and three-year exclusivities.

A case in point is newly-separated enantiomer products.[113] When a drug company decides to market a single enantiomer version of its racemate drug, the question is

[104] The application here is necessarily a 505(b)(2) application, because a second applicant cannot file a 505(j) generic application before a first NDA has been approved.

[105] *See* FDA, Proposed ANDA Rule, *supra* note 86, at 28,901.

[106] 21 U.S.C. §§ 355(c)(3)(D)(ii) and 355(j)(5)(D)(ii).

[107]

> According to 21 C.F.R. § 210.3(b)(7), an active ingredient is any component of a drug product intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of humans or other animals. Active ingredients include those components of the product that may undergo chemical change during the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect.

FDA, About the Inactive Ingredients Database, *at* http://www.fda.gov/cder/iig/iigfaqWEB.htm (last visited Feb. 15, 2005).

[108] According to FDA terminology, "[a] new chemical entity means 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," while an active moiety is defined as a "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." FDA, FAQs on Exclusivity, *supra* note 70, questions 8 and 9. In theory, a NCE could be an "old" drug provided it has never successfully gone through the 505(b)(1) or 505(b)(2) marketing approval process.

[109] *See* FDA, 505(b)(2) Draft Guidance, *supra* note 3, at 7; CDER, FDA, Prussian Blue Drug Products-Submitting a New Drug Application, Guidance for Industry, at 5 (Jan. 2003), *at* http://www.fda.gov/cder/guidance/5506fnl.pdf (last visited Feb. 15, 2005).

[110] *See* FDA, 505(b)(2) Draft Guidance, *supra* note 3, at 7-8.

[111] *See* 21 C.F.R. § 314.108(a); FDA, 1994 ANDA Final Rule, *supra* note 69, at III.J., cmt. 97.

[112] *See, e.g.,* Michael Strong, *FDA Policy and Regulation of Stereoisomers: Paradigm Shift and the Future of Safer, More Effective Drugs*, 54 FOOD & DRUG L.J. 463, 483 (1999).

[113] Enantiomers are a type of stereoisomers constituted of two identical molecules but for the fact that each is the mirror image of the other; like two hands, they are mirror images but cannot be superimposed. When a drug contains both enantiomers, it is called a racemate or racemic. Not all molecules have enantiomers; those that do are called chiral molecules. In some drugs, one enantiomer exhibits positive quality, while the other enantiomer is responsible for adverse reactions or is simply inactive; in those cases, selling a drug made only of the "good" enantiomer presents therapeutic benefits. *See also Do Single Stereoisomer Drugs Provide Value*?, 45 THERAPEUTICS LETTER (June/Sept. 2002) (probing whether single enantiomers really offer such benefit), *at* http://www.ti.ubc.ca/PDF/45.pdf (last visited Feb. 15, 2005). *See also generally* Strong, *supra* note 112, at 466-71.

whether this product is held to be an NCE or just a new formulation of an existing active moiety. FDA has long asserted that enantiomers are not NCEs and therefore can receive, at best, only a three-year exclusivity (*see infra* Part III.A.2.).[114] In 1997, the agency signaled that it was contemplating a possible change to its interpretation,[115] although it has not yet acted upon its proposal.

The reactions to the 1997 proposal have been mixed. The generic industry contends that the current FDA process confers sufficient benefits to sponsors.[116] One author, for instance, chided the agency for its illogical stance: "When the FDA has already approved the sale of a racemic compound, it strains logic to suggest that an enantiomer already marketed within the racemate is a new compound when sold alone."[117] In the meantime, brand-name pharmaceutical firms have come under criticism for using enantiomers to "evergreen" their monopolies.[118] When separating enantiomers and identifying the most potent one is a straightforward task,[119] rewarding this exercise with a five-year exclusivity would run against the public policy objectives underlying this exclusivity (i.e., to encourage the development of entirely new products). Moreover, the agency already asks that pharmaceutical sponsors automatically test chiral drugs to identify the "good" enantiomer.[120] Pharmaceutical firms also minimize their liability towards patients by removing the "bad"[121] enantiomer (i.e., the one causing adverse reactions).[122] If firms already are obligated to develop a single enantiomer version of their compounds, there is no imperative to bestow longer exclusivity rewards on them. Finally, the agency requires less extensive studies to support marketing applications for single enantiomers, and it reviews these applications rapidly.

3. *Innovation and Efforts?*

As explained above, the law imposes only one requirement for the five-year marketing exclusivity to be granted: that the drug be an NCE. Hence, the drug product need not

[114] *See* FDA, Proposed ANDA Rule, *supra* note 86; FDA, 1994 ANDA Final Rule, *supra* note 69, at III.J, cmt 105. *See also* Thomas J. Parker et al., *FDA Marketing Exclusivity for Single Enantiomers of Previously Approved Racemates*, INTELLECTUAL PROPERTY & TECH. L.J. (Jan. 2003), *at* http://www.coudert.com/publications/articles/030115_30_enantiomers_ipt.pdf (last visited Feb. 15, 2005).

[115] *See* FDA, Policy on Period of Marketing Exclusivity for Newly Approved Drug Products With Enantiomer Active Ingredients, Request for Comments, 62 Fed. Reg. 2167 (Jan. 15, 1997). *See also* Dickinson, *supra* note 59, at 200-01; Strong, *supra* note 112, at 479-86.

[116] "Enantiomers of existing drugs qualify for an additional twenty years of patent protection if it can be shown that the enantiomer exhibits unanticipated characteristics [e.g., Prozac]. […] While the patentability of these compounds raises troublesome policy issues, the willingness of the PTO to grant patent protection for purified enantiomers creates major incentives for their production." Steven C. Carlson, *The Case Against Market Exclusivity for Purified Enantiomers of Approved Drugs*, 1 YALE SYMP. L. & TECH. 6 (1999).

[117] *Id*. at 6.

[118] Lara J. Glasgow, *Stretching the Limits of Intellectual Property Rights: Has the Pharmaceutical Industry Gone Too Far?*, 41 J.L. & TECH. 227, 250 (2001).

[119] FDA noted "that technological advances (large-scale chiral separation procedures or asymmetric syntheses) permit production of many single enantiomers on a commercial scale . . . ." CDER, FDA, FDA's Policy Statement for the Development of New Stereoisomeric Drugs (May 1, 1992), *available at* http://www.fda.gov/cder/guidance/stereo.htm (last visited Feb. 15, 2005).

[120] *See, e.g.,* CDER, FDA, Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances (Feb. 1987), *at* http://www.fda.gov/cder/guidance/drugsub.pdf (last visited Feb. 15, 2005); CDER, FDA, FDA's Policy Statement for the Development of New Stereoisomeric Drugs (May 1, 1992), *at* http://www.fda.gov/cder/guidance/stereo.htm (last visited Feb. 15, 2005); CDER, FDA, Draft Guidance, Analytical Procedures and Methods, Validation Chemistry, Manufacturing, and Controls Documentation (Aug. 2000), *at* http://www.fda.gov/cder/guidance/2396dft.pdf (last visited Feb. 15, 2005). *See also* Strong, *supra* note 112, at 475-79.

[121] Not all chiral drugs have a "bad" enantiomer. *See* note 113 *supra*.

[122] *See* Carlson, *supra* note 116, at 6.

constitute an innovation. At least in theory, a new drug that is quite obvious can nonetheless benefit from the five-year protection—assuming that no one submitted before this "evident" idea to FDA. It is not necessary that the drug represent a significant therapeutic advance. The drug may address, for example, a benign medical condition (e.g., baldness); it also may add to an already-plentiful arsenal of existing drugs for the same condition, without offering any significant advantage over existing treatments.

A five-year exclusivity is granted to an NCE even if the drug development did not involve any clinical trials conducted by its sponsor. Although this occurs rarely, one can imagine a situation where the NDA sponsor did not personally carry out, or finance, the necessary clinical trials.

C. *The Three-Year Marketing Exclusivity*

1. *Legal Basis and Consequences*

The legal basis for the three-year exclusivity is 21 U.S.C. §§ 355(c)(3)(D)(iii), (iv) and 355(j)(5)(D)(iii), (iv).[123] Contrary to the five-year exclusivity, FDA can receive and review applications by second applicants (i.e., 505(j) ANDA applicant and 505(b)(2) NDA applicant) before the three-year exclusivity has expired. It can even grant tentative approval, but the approval becomes effective only after the three-year period has elapsed.[124] The second applicant can thus market its product immediately following expiry of the three-year exclusivity. This difference set aside, the effects of the three-year exclusivity are very similar to those of the five-year exclusivity (as described in Part III.B.1.a. *supra*).

The three-year exclusivity can benefit both NDAs[125] and supplements to NDAs.[126] The holder of an NDA has to file a supplemental NDA (sNDA) if it wants to market a modified version of its drugs;[127] all major changes brought by an NDA holder to an already-approved drug require the prior approval of an sNDA.[128] Such changes include new indications for the same drug (e.g., colon cancer in addition to breast cancer), new dosage forms (e.g., tablet in addition to syrup),[129] new strengths[130] (e.g., 30 mg in addi-

[123] 21 U.S.C § 355(c), *at* http://www4.law.cornell.edu/uscode/21/355.html (last visited Feb. 15, 2005) corresponds to FDCA § 505, *at* http://www.fda.gov/opacom/laws/fdcact/fdcact5a.htm (last visited Feb. 15, 2005); 21 U.S.C. § 355(j) corresponds to FDCA § 505(j).

[124] *See* Dickinson, *supra* note 59, at 201.

[125] *See* FDCA § 505(c)(3)(D)(iii) regarding 505(b)(2) application; FDCA § 505(j)(5)(D)(iii) regarding 505(j) ANDA application.

[126] *See* FDCA § 505(c)(3)(D)(iv) regarding 505(b)(2) application; FDCA § 505(j)(5)(iv) *re* ANDA. FDA defines a supplement as a "marketing application submitted for changes in a product that already has an approved NDA. FDA must approve all important NDA changes (in packaging or ingredients, for instance) to ensure that the conditions originally set for the product are not adversely affected." FDA, A Drug Review Glossary, *at* http://www.fda.gov/fdac/special/newdrug/bengloss.html (last visited Feb. 15, 2005).

[127] On the contrary, a company files an NDA (or a 505(b)(2) application) if it wants to modify a drug to which it does not hold the initial NDA.

[128] *See* 21 C.F.R. § 314.70 (ascribing changes to three categories). A supplement to an NDA falls into the NDA category. *See* 21 C.F.R. § 314.71; *see also* FDA, 505(b)(2) Draft Guidance, *supra* note 3, at 1; CDER, FDA, Guidance for Industry, Changes to an Approved NDA or ANDA (Apr. 2004) (regarding changes pertaining principally to the manufacturing process), *at* http://www.fda.gov/cder/guidance/3516fnl.pdf (last visited Feb. 15, 2005).

[129] For a list of possible dosage forms, see FDA, THE NATIONAL DRUG CODE DIRECTORY, *at* http://www.fda.gov/cder/ndc/tbldosag.txt (last visited Feb. 15, 2005). The possibilities notably include emulsion, gel, pill, spray, patch, and tincture.

[130] *See* 21 C.F.R. § 210.3(b)(16), *available at* http://www.gmp1st.com/drreg.htm#210.3 (last visited Feb. 15, 2005).

tion to 10 mg), new routes of administration (e.g., injectable drug in addition to oral form),[131] new patient population,[132] and new conditions of use (e.g., new dosage schedule).[133] Only changes implemented through an NDA or a supplement may give rise to the three-year exclusivity.[134] The three-year exclusivity is not reserved to research-based pharmaceutical companies; second entrants marketing similar versions of existing drugs also can receive it if they submit their own data to support an application, typically a 505(b)(2) application.[135]

Three other conditions must be met for a company to benefit from this three-year exclusivity: it must have (i) conducted or sponsored (ii) clinical trials (iii) which were essential for the approval of the application or of the supplement.

2. *Role of the Exclusivity Holder in the Clinical Development*

To be eligible for the three-year exclusivity, the applicant must have either personally sponsored the study[136] or provided considerable support. A drug sponsor is the party who officially "takes responsibility for and initiates a clinical investigation;"[137] this involvement goes beyond simply supplying the drug product being tested.[138] An applicant is deemed to have provided considerable support if it financed at least fifty percent of the study's cost;[139] a "certified statement from a certified public accountant" must establish that support.[140] FDA does not verify such statements.[141] If the applicant has financed less than fifty percent of the clinical trial cost, but still wants to benefit from the exclusivity, it must explain why it deserves that benefit.[142] Such an explanation may relate to extremely expensive studies or to nonfinancial contributions on the part of the sponsor.[143] Even if the applicant were not the initial sponsor or "financier," it can claim

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[131] For a list of possible routes of administration, see FDA, THE NATIONAL DRUG CODE DIRECTORY, at http://www.fda.gov/cder/ndc/tblroute.txt (last visited Feb. 15, 2005).

[132] FDA letter to Mr. Mahn, *supra* note 81, at 2.

[133] "FDA expects that only those changes in an approved drug product […] would be granted exclusivity. These are the types of changes in a drug product that require prior approval by FDA before the change may be made." FDA, Proposed ANDA Rule, *supra* note 86, at subpt. L.1.b.iv. New efficacy information in the drug's label also qualifies for exclusivity. *See, e.g.,* FDA's letter to Mr. Labson and Ms. Walsh (counsel for Wyeth) in response to their petition (Sept. 20, 2004), *at* http://www.fda.gov/ohrms/dockets/dailys/04/oct04/100504/03p-0518-pav00001-vol1.pdf (last visited Feb. 24, 2005).

[134] For example, changes in the drug's labeling, such as the mention of a new risk warning, are not entitled to the three-year exclusivity. *See* FDA, 1994 ANDA Final Rule, *supra* note 69, at III.J., cmt. 95.

[135] *See* FDA, 505(b)(2) Draft Guidance, *supra* note 3, at 7.

[136] Such sponsor has to be named in Form FDA-1571. *See* online form, *at* http://www.fda.gov/opacom/morechoices/fdaforms/FDA-1571.pdf (last visited Feb. 24, 2005).

[137] See Instructions to Fill Out Form FDA-1571, *at* http://www.fda.gov/cder/forms/1571-1572-help.html (last visited Feb. 15, 2005).

[138] *Id*.

[139] 21 C.F.R. § 314.108(a). *See also* FDA, 1994 ANDA Final Rule, *supra* note 69, at III.J., cmt. 98.

[140] 21 C.F.R.§ 314.108(a).

[141]

> The agency acknowledges that it does not possess expertise and record*s* essential to determining what elements should properly be considered in determining the cost of a study and what constitutes 50 percent funding of that study. The agency does not ordinarily intend to substitute its judgment for that of the applicant with respect to the 50 percent threshold. The agency will only look to see if the investigations were conducted under an IND in which the applicant was the sponsor or that the application contains the certification with supporting information.

FDA, Proposed ANDA Rule, *supra* note 86, at sec. L.1.b.iv.

[142] 21 C.F.R. § 314.50(j)(4)(iii). *See also* FDA, 1994 ANDA Final Rule, *supra* note 69, at III.J., cmt. 98.

[143] "Merely supplying the drugs or providing other in kind support would not normally constitute 'conducting or sponsoring' a study." FDA, Proposed ANDA Rule, *supra* note 86, at sec. L.1.b.iv.

the exclusivity if it buys the exclusive rights to the completed clinical trial.[144] Because the applicant has to obtain the exclusive rights, no other person will be entitled to the exclusivity. Finally, when two pharmaceutical companies merge, the resulting entity automatically acquires the right to the studies of its "predecessor in interest."[145]

3. *A New Clinical Trial*

The study under consideration must consist of one or several clinical trial(s) on human subjects; this excludes animal experimentation and laboratory work (i.e., preclinical studies). The clinical study cannot simply be a compilation of already-available scientific literature (e.g., meta-analyses). Also excluded from the definition of clinical investigations, according to 21 U.S.C. § 355, are bioavailability (BA) and bioequivalence (BE) studies. These types of studies examine how the human body absorbs a compound,[146] respectively whether one compound is absorbed in a similar way as another compound.[147] BE studies ordinarily are required for ANDAs because, as a condition of approval, the generic drug must be shown to be bioequivalent to the reference listed drug.[148] BA and BE studies also are performed in other contexts (e.g., if a brand-name manufacturer wants to sell a new formulation of its drug, it will want to verify that the two drugs are similarly absorbed).[149]

The clinical trial also must be "new" in the sense that it cannot be one already submitted to obtain FDA approval for the same or for a different drug.[150] Neither can it be a repetition or copy of previously-submitted trials. If the applicant initially submitted the study to support the *safety* of its drug, however, it can submit it again to support its *effectiveness*.[151] The time period during which the clinical trial took place is irrelevant, as "new" is not interpreted as a "temporal requirement."[152] Therefore, a sponsor can use an "old" study, provided the latter was never before submitted to FDA. Apparently, nothing prevents drug sponsors from submitting as "new studies" studies that previously were submitted to foreign drug agencies. It is not required that the clinical trial have taken place on U.S. territory; a "foreign" clinical study also can prompt exclusivity.

4. *An Essential Clinical Trial*

For the sponsor to get the three-year marketing exclusivity, the clinical study submitted to FDA must be essential for the approval of the sponsor's application. If the study

[144] 21 C.F.R. § 314.108(a). *See also* FDA, FAQs on Exclusivity, *supra* note 70, question 10. *See also* FDA, 1994 ANDA Final Rule, *supra* note 69, at III.J., cmt. 98 (pointing out that publicly-funded studies generally will not be available for transfer of exclusive rights).

[145] 21 C.F.R. § 314.50(j)(4)(iii).

[146] "The term "bioavailability" means the rate and extent to which the active ingredient or active moiety is absorbed from a drug product." 21 C.F.R. § 320.1(a).

[147] A generic drug is bioequivalent to the reference drug if the rate and extent of absorption (i.e., its availability at the site of drug action) does not differ significantly from that of the reference product, "when administered at the same molar dose under similar conditions in an appropriately designed study." *Id*. § 320.1(e). The two drugs also are considered bioequivalent if the significant difference in rate and extent of absorption is intentional, is not essential to the effectiveness of the drug and is deemed medically insignificant; in that case, the difference must be indicated in the drug's label. *Id*. "One way scientists demonstrate bioequivalence is to measure the time it takes the generic drug to reach the bloodstream in 24 to 36 healthy volunteers." FDA, ANDA Process for Generic Drugs, *available at* http://www.fda.gov/cder/regulatory/applications/anda.htm#Forms (last visited Feb. 15, 2005) [hereinafter FDA, ANDA Process for Generics].

[148] *See* 21 C.F.R. § 314.94.

[149] "Brand-name drugs are subject to the same bioequivalence tests as generics upon reformulation." FDA, ANDA Process for Generics, *supra* note 147.

[150] *See* FDA, 1994 ANDA Final Rule, *supra* note 69, at III.J., cmt. 101.

[151] 21 C.F.R. § 314.108(a) (defining new clinical investigation).

[152] FDA, FAQs on Exclusivity, *supra* note 70, question 7. *See also* FDA, 1994 ANDA Final Rule, *supra* note 69, at III.J., cmt. 101.

is simply interesting, helpful, or supportive—without being essential— its sponsor is not eligible for the three-year exclusivity.[153] Similarly, if FDA already holds enough information to determine that the drug is safe and effective, then there is no room left for essential clinical trials.[154]

The sponsor must provide FDA with "a list of all published studies or publicly available reports of clinical investigations known to the applicant through a literature search."[155] The applicant must certify that, to the best of his knowledge, the list is "complete and accurate,"[156] and must explain why the listed studies are insufficient to support its application.[157] FDA does not provide advance confirmation as to what studies it will consider essential for approval.[158] The sponsor bears the risk of conducting a study that would be deemed useful, but not essential. The sponsor can minimize this risk by discussing in advance the type of trial design required; however, the agency will not commit itself.[159]

Even though the statute speaks of clinical investigations (in the plural form), one clinical study can be sufficient to warrant marketing exclusivity.[160] In recent years, FDA has been charged with "raising the bar" as to the level of clinical evidence necessary to achieve demonstration of safety and efficacy; hence, in practice, a single clinical trial may not suffice to secure approval of the NDA or of the supplement.

Initially, it was believed that marketing exclusivity would reward only significant innovation that required "a considerable investment of time and money."[161] While it may be reasonably presumed that this requirement is fulfilled in the case of NCEs,[162] there cannot be any such automatic presumption for non-NCEs. In its 1989 proposed rule on ANDA regulations, FDA repeatedly stressed that drugs rewarded by a three-year exclusivity had to bring "significant changes" or "significant innovations."[163] Likewise, in its 1994 Final Rule, FDA insisted that the clinical investigations be "vital to the application or supplement."[164] FDA did not identify a mechanism, however, to enforce this admittedly vague requirement.[165] Provided that the clinical trial is essential to validate the modification of the drug product, exclusivity will be awarded.

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[153] *See* Dickinson, *supra* note 59, at 201.

[154] FDA, Proposed ANDA Rule, *supra* note 86.

[155] 21 C.F.R. §314.50(j)(4)(ii). *See also* FDA, 1994 ANDA Final Rule, *supra* note 69, cmt. 14.

[156] *See also* FDA, 1994 ANDA Final Rule, *supra* note 69, cmt. 14.

[157] *Id*.

[158] *See* FDA, Proposed ANDA Rule, *supra* note 86, at 28,900-01; FDA, 1994 ANDA Final Rule, *supra* note 69, cmt. 14.

[159] *See* FDA, 1994 ANDA Final Rule, *supra* note 69, cmt. 14.

[160] *Id*.

[161] *Id*.

[162] According to the FDA, NCEs "by definition are innovative." *Id*. *See also* FDA, FAQs on Exclusivity, *supra* note 70.

[163] FDA, Proposed ANDA Rule, *supra* note 86, at sec. L.1. FDA wrote:

> Congress understood that the substantial economic rewards of exclusivity might well encourage drug companies to make *minor and unimportant alterations* in their marketed drug products or to conduct *additional* tests which they could claim provide important new information about a marketed drug product. To avoid rewarding such behavior, the 3-year provision includes the special criteria intended to restrict eligibility to significant innovations.

Id. (emphasis added).

[164] *See* FDA, 1994 ANDA Final Rule, *supra* note 69, at III.J., cmt. 95.

[165] *See* Generic Pharmaceutical Association's (GPhA's) Reply and Submission to FDA, Symposium on the Hatch-Waxman Act, at 18 (Jan. 30, 2002), *at* http://www.fda.gov/cder/ogd/GPHA_Reply_FINAL1.pdf (last visited Feb. 15, 2005).

5. *Limitations*

An important limitation of the three-year exclusivity is that it protects only the new "addition" to the drug, and not the already-approved aspects of the drug.[166] For example, if a company files a supplement for a new use for its existing drug, only that new use will be protected from generic competition; competitors remain free to market the drug for all of its previous indications—provided, of course, that the other relevant patents or exclusivities have expired.[167] When the same drug (in the same dosage form, strength, and route of administration) has dual uses with only one of them being protected by the three-year exclusivity, the latter may not afford much protection against competition. Although the generic firm is not allowed to market or advertise the drug for that new use, physicians and/or patients may choose to prescribe and/or use the generic version of the drug also for the new use. Even though the generic label cannot mention that new use, the identity between the two products, as well as their price difference, will not escape the physician's attention.[168]

It is not surprising that innovator firms have criticized what they see as a loophole in the three-year marketing exclusivity. One brand-name company claimed that FDA should not approve an ANDA when the generic firm's implicit intentions—despite its explicit label[169]—is to market its drug for the new (and therefore protected) indications.[170] The pioneer firm, Sigma-Tau, pointed out that the bulk of the demand for the drug was aimed primarily toward the new (and not the old unprotected) indication; it asserted that the generic competitor had asked for an ANDA only for the route of administration (i.e., injectable form) that could also be used in relation with the new indication.[171] Even more importantly, Sigma-Tau complained that the federal and state governments would reimburse the generic drug also for the new indication; hence, Sigma-Tau might be entirely unable to sell its drug for the new indication to Medicaid patients.[172] The Court of

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[166] *See* Dickinson, *supra* note 59, at 201. However, exceptionally, when the three-year exclusivity was granted as a reward for new efficacy and safety related information supplied by the pioneer firm, the second entrant may be barred from receiving marketing approval for the old version, because selling the old drug version without the new (and exclusivity-protected) information would threaten patients' safety. *See, e.g.*, FDA's letter to Mr. Labson and Ms. Walsh, *supra* note 133, at 3-4. A different legal standard however applies to pediatric safety/efficacy information generated by the pioneer; such information may in certain circumstances be "copied" by the second entrant even though the information is protected by pediatric exclusivity. *See, e.g.*, FDA's letter to Mr. Mahn, *supra* note 81, 11-14.

[167] Even if part of the data supporting the new and old indication of the drug are identical, the generic firm will be able to rely on the entire file submitted in support of the "old" NDA.

[168] American physicians are at liberty to prescribe a drug for uses or in ways that are not described in its label.

[169] The label of the generic drug can mention only the unprotected indications, and cannot include the new indications protected by the pioneer company's three-year marketing exclusivity. The same is true for other aspects of the drug currently protected by marketing exclusivity.

[170] Sigma-Tau Pharmaceuticals v. Schwetz, 288 F.3d 141 (4th Cir. 2002).

> Sigma-Tau contends that the FDA was obligated to look beyond the labeling to what Sigma-Tua maintains is the reality of the situation, which is that most of the need for the generics—and thus most of the money to be made—lies in treating patients with ESRD [the disease treated by the new indication].

Id. at 147.

[171] *Id*. at 145.

[172] *Id*. This also was an important issue in *Bristol-Myers Squibb v. Shalala*, 91 F.3d 1493, 1496 (D.C. Cir. 1996). In that case, the Court of Appeals for the District of Columbia acknowledged that the innovator company, Bristol-Myers Squibb (BMS), might suffer a prejudice due to the fact that insurers would prefer to reimburse only the cheaper generic drug, even when used for the protected indication supposedly reserved to the pioneer drug. It wrote:

> BMS claims that economic reality renders the protection offered by the Secretary largely an illusion. Perhaps so, but why? By BMS's own account, it is because the value of the protection the Congress most clearly conferred upon pioneers would be greater but for some state laws and health insurers that mandate substitution of generic drugs. That is not a sufficient basis upon which to conclude that the Congress intended to confer upon the manufacturers of pioneer drugs the much broader protection that BMS now seeks.

Id. at 1500.

Appeals for the Fourth Circuit confirmed the opinion of the lower court, holding that the statute clearly supported the grant of an ANDA in these circumstances. Furthermore, it considered that FDA's interpretation of the statute was reasonable. The court found that, at the early stage when the ANDA is about to be granted, FDA should not have to examine circumstances other than the official label applied for by the generic company. Only if subsequent circumstances showed that the generic manufacturer truly intended to market its product for the new protected indication, could FDA reconsider its ANDA approval.[173] At the pre-approval stage, the agency did not have "to assume bad faith on the part of" the generic manufacturer.[174] The court also criticized Sigma-Tau for opposing competition by asking that "foreseeable off-label use […] bar the approval of generic drugs, even for unprotected indications."[175]

While the above-mentioned case was concerned with orphan drug exclusivity, at least one other court has reached the same outcome for the three-year marketing exclusivity. In *Bristol-Myers Squibb v. Shalala*,[176] the Court of Appeals for the District of Columbia also upheld FDA's approval of an ANDA for an old unprotected indication of the pioneer/reference product that recently had obtained a three-year marketing exclusivity for a new indication. These decisions have fully upheld the agency's longstanding interpretation.[177]

D. *Convergence With the European Union?*

The U.S. research-based pharmaceutical industry and its supporters regularly call attention to the longer exclusivity period available in the European Union. They call for U.S. marketing exclusivity periods to be extended to match the ten-year period of European data protection.[178] They contend that the U.S. pharmaceutical industry suffers from a competitive disadvantage because drugs sold in the United States benefit from a much shorter five-year exclusivity period. Some even have argued—unconvincingly in this author's view—that the GATT/TRIPS Agreements oblige the United States to harmonize its system with the European one.[179]

[173] *Compare* Allergan, Inc. v. Alcon, 324 F.3d 1322 (Fed. Cir. 2003) *and* Warner-Lambert Co. v. Apotex Corp., 316 F.3d 1348, 1354-55, 1364 (Fed. Cir. 2003) (cases where the patent and NDA holder sued the generic applicant for induced patent infringement).

[174] *Sigma-Tau Pharm.*, 288 F.3d at 148.

[175] *Id*. at 147.

[176] 91 F.3d at 1496 (D.C. Cir. 1996). The crux of this case differs somewhat from the *Sigma-Tau* case. The *BMS* case rested essentially on the question of whether the generic drug could have a different label than the reference drug, due to the fact that it did not mention the new and protected indication approved exclusively for the benefit of the pioneer drug.

[177]

> Thus, if the innovation relates to a new active moiety or ingredient, then exclusivity protects the pioneer drug product from other competition from products containing that moiety or ingredient. If the innovation is a new dosage form or route of administration, then exclusivity protects only that aspect of the drug product, but not the active ingredients. If the innovation is a new use, then exclusivity protects only that labeling claim and not the active ingredients, dosage form, or route of administration.

FDA, Proposed ANDA Rule, *supra* note 86, sec. L.1.

[178] For example, Senator Hatch said:

> In contrast [to the American five-year exclusivity], it is my understanding that most European nations and Japan have adopted a ten-year data exclusivity rule. Why not consider harmonizing and move to the European standard for this important information which, but for Hatch-Waxman, would be considered proprietary information?

107th Cong., 148 CONG. REC. S 7875 (Aug. 1, 2002), at 78,777.

[179] *Appendix E: BIO Supported Amendments to the Hatch-Waxman Patent Term Restoration Act, Before the Courts and Intellectual Property Subcomm. of the House Judiciary Comm.* (Feb. 26, 1997) (testimony of Chuck Ludlam, Vice Pres., Gov't Relations, Biotechnology Industry Organization (BIO)), *at* http://judiciary.house.gov/legacy/4125.htm (last visited Feb. 24, 2005).

The U.S. pharmaceutical industry fails to take into account several characteristics of the current E.U. data protection system. First, presently and until November 2005, only drugs approved by the European Medicines Agency (EMEA) through the centralized procedure receive a ten-year period of protection; for drugs approved through the mutual recognition procedure, many Member States still apply either a six-year or a ten-year protection period. About half of the European countries have apply the six-year period.[180] The countries that selected the ten-year alternative typically are those that host an important local pharmaceutical industry.[181] Second, the European Union grants little or no protection to line extensions. In other words, there is no European equivalent to the U.S. three-year marketing exclusivity.

All in all, the two regulatory regimes should be viewed as roughly equivalent in that neither one confers significantly broader protection to pioneer drugs. Finally, as a Canadian Federal Court observed, even five years of exclusivity can represent a windfall for research-based firms: "[I]n the pharmaceutical industry, new drugs are being developed all the time, and a period of five years is a long time to grant a *de facto* monopoly for a drug that is not protected by a patent. After five years, many drugs will have been superseded by more effective products."[182]

IV. DATA EXCLUSIVITY IN THE EUROPEAN UNION

A. *Legal Basis and Origin of Data Exclusivity*

In the European Union, marketing exclusivity is referred to as data protection or data exclusivity. The European Union introduced data protection in 1986 through the 87/21/EEC Directive,[183] which amended the 65/65/EEC Directive.[184] Historically, data exclusivity was introduced to afford some degree of protection to research-based pharmaceutical companies in European Member States that did not confer patents to pharmaceuticals.[185] For example, until 1992, Spain and Portugal did not grant product patents to medicinal products.[186] Today, all E.U. countries

[180] These countries are Austria, Denmark, Finland, Greece, Ireland, Portugal, and Spain. *See* European Commission, Notice to Applicants, Procedures for Marketing Authorization, Vol. 2A, Ch. 1, Marketing Authorization, at 14 (updated Feb. 2004), *at* http://pharmacos.eudra.org/F2/eudralex/vol-2/A/v2a_chap1%20_r2_2004-02.pdf (last visited Feb. 15, 2005) [hereinafter European Commission, Vol. 2A.1.]. In addition, Iceland and Norway, which belong to the European Economic Area, also apply the six-year minimum period, while Liechtenstein follows the Swiss practice. *See* TREVOR M. COOK, THE PROTECTION OF REGULATORY DATA IN PHARMACEUTICAL AND OTHER SECTORS 30 (Sweet & Maxwell 2000).

[181] *See* subpt. IV.B.1.d. *infra*. *See also* European Commission, Vol. 2A.1., *supra* note 180, at 14.

[182] Bayer, Inc. v. Canada (Attorney General), 1 F.C. 553, 581 (1998).

[183] Council Directive 87/21/EEC of 22 December 1986 Amending Directive 65/65/EEC on the Approximation of Provisions Laid Down by Law, Regulation, or Administrative Action Relating to Proprietary Medicinal Products, *at* http://ikev.org/docs/eu/387L0021.htm (last visited Feb. 15, 2005). Member countries had until July 1987 to implement this Directive; except for Greece, Spain, and Portugal, which were given an extension until January 1, 1992.

[184] *See* Art. 4.8(a)(iii) of Council Directive 65/65/EEC.

[185] Jamie Love, TACD on Pharmaceutical Registration Data Exclusivity (Draft), *at* http://lists.essential.org/pipermail/pharm-policy/2000q1/000059.html (last visited Feb. 15, 2005).

[186] *See* Pascual Segura, European Generic Med. Ass'n, *The Peculiar Patent and Generic Situation in Spain*, at 24, *at* http://www.imim.es/jcami/material/3Segura%20-%20UPF%20Documentació.pdf (last visited Mar. 31, 2004) ("Spain joined the European Patent Convention in 1986 but, as in Greece and Portugal, pharmaceutical products are patentable from October 8, 1992, the day following the expiry of a transitional period according to Article 167 EPC.") In Spain and Portugal, however, because of the delay between the grant of patent protection and the grant of marketing authorization, the first patented drugs appeared on these two markets around 2002. Segura, *supra* note 186.

grant strong—and mostly uniform—patent protection to pharmaceutical inventions.[187]

Directive 65/65/EEC, as well as several others, were consolidated in 2001 in a single Code, Directive 2001/83/EC.[188] Presently Article 10.1(a)(iii) of this Code governs European data exclusivity. This provision, along with several others, was revised in 2004.[189] Because the changes will become effective only for new drugs applying for marketing authorization after the implementation date of the revised Directive 2001/83/EC (October 30, 2005), both the current and the future systems need to be analyzed.

B. *The Current System*

1. *Duration of E.U. Data Exclusivity*

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.[190] Directive 2001/83/EC currently provides for four different lengths of exclusivity: a ten-year mandatory period; a six-year minimum period; a six-year minimum period capped by the patent duration; and a ten-year optional period.

a. *The Ten-Year Mandatory Period*

The ten-year mandatory period shields pharmaceuticals (referred to as "medicinal products" in E.U. terminology) that are approved by the London-based EMEA through the centralized procedure.[191] Presently, only so-called "high-tech" products are eligible for approval through this centralized procedure.[192] On one hand, these are drugs de-

[187] See further project of Council regulation on the community patent, Preparation of the Meeting of the Council on 11 March 2004 (7119/04 7119/04) (7119/04) (Mar. 8, 2004), *at* http://register.consilium.eu.int/pdf/en/04/st07/st07119.en04.pdf (last visited Feb. 24, 2005).

[188] The 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 [hereinafter Directive 2001/83/EC] repealed and replaced Directive 65/65/EEC. The text of Directive 2001/83/EC, 2001 O.J. (L 311) 67, *at* http://pharmacos.eudra.org/F2/pharmacos/docs/Doc2001/nov/Codifications/HumanCode2001-83/2001-83EN.pdf (last visited Feb. 15, 2005). 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, *at* http://pharmacos.eudra.org/F2/eudralex/vol-1/new_v1/direct_comm_2003_63_en.pdf (last visited Feb. 15, 2005).

[189] *See infra* discussion in Part IV.D.

[190] For medicinal products approved under the centralized procedure, data protection starts with the E.U. marketing authorization decision. *See also* Kingham & Castle, *supra* note 37, at 215.

[191] Art. 10.1.(a)(iii) of Directive 2001/83/EC (medicinal products approved through the centralized procedure obtain a single marketing authorization valid in all Member States). The authorization takes the form of a Commission decision, following assessment by committees created within the EMEA. *See also* 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 (last visited Feb. 15, 2005).

[192] *See* Council Regulation (EEC) No 2309/93 of 22 July 1993 Laying Down Community Procedures for the Authorization and Supervision of Medicinal Products for Human and Veterinary Use and Establishing a European Agency for the Evaluation of Medicinal Products, *at* http://pharmacos.eudra.org/F2/eudralex/vol-5/pdfs-en/932309en.pdf (last visited Feb. 15, 2005).

The 2001 Pharma Review also has led to the revision of this Regulation to broaden the categories of medicinal products that must follow the centralized procedure (particularly treatments against AIDS, cancer, diabetes, neurodegenerative disorders, and—after a four-year waiting period—treatments against auto-immune diseases, immune dysfunctions, and viral diseases). *See* Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (*OJ L 136, 30/4/2004, at 1-33*), *at* http://pharmacos.eudra.org/F2/eudralex/vol-1/REG_2004_726/REG_2004_726_EN.pdf at whereas (8) and point 1 of Annex. Most provisions of this Regulation will become effective no later than November 20, 2005.

[193] *See* Council Regulation 2309/93, Part A of Annex I.

rived from biotechnology (e.g., recombinant DNA)[193], and, on the other hand, products deemed to represent a significant innovation or therapeutic advance.[194] The latter category includes new active substances, new therapeutic indications, new delivery systems, and new manufacturing methods. Whereas drugs belonging to this second category can use *either* the centralized procedure[195] or the mutual recognition procedure,[196] drugs belonging to the first category (i.e., biotechnology products) *must* be approved through the centralized procedure.[197]

b. *Six-Year Minimum Period*

The six-year minimum period applies to all other drugs (i.e., drugs approved through either the mutual recognition procedure or the national procedure of an individual Member State). A Member State can apply its national procedure to approve medicinal products provided that the latter will be sold only on the domestic market; drugs marketed in several Member States must go through the mutual recognition (i.e., decentralized) procedure, unless they are eligible for the centralized procedure.[198]

c. *Six-Year Period Capped by Patent*

Member States that apply the six-year minimum period[199] may choose to cap this period at the instant the patent protecting the drug expires.[200] If a supplementary protection certificate (SPC) extends the duration of the patent, then the cap sets in when the SPC expires.[201] Three countries—Greece, Spain, and Portugal—have opted for this solution.[202] In situations where a drug is protected by several patents, the Directive does not indicate which of them must have expired to put an end to the data exclusivity.[203]

d. *Ten-Year Optional Period*

Member States can decide to extend the six-year period of protection up to a ten-year ceiling. Member States have the choice only between six-year and ten-year periods, and cannot choose an intermediate period of protection (e.g., seven years). Moreover, this extension must benefit all eligible pharmaceuticals marketed on their territory; discrimination on the basis of the country of origin is prohibited.

According to the letter of the 2001/83/EC Directive, this decision should be based on a finding that the extension is "necessary in the interest of public health."[204] The stan-

[194] *See id*., Part B of Annex I.

[195] Art. 3.2. of Council Regulation 2309/93. The drug sponsor/applicant—noted in the Regulation as "[t]he person responsible for placing on the market a medicinal product"—must make a request if it wants to follow the centralized procedure.

[196] On the requirements of the mutual procedure, see European Commission, Notice to Applicants, Vol. 2A., Procedure for Marketing Authorizations, ch. 2, Mutual Recognition (June 2004), *at* http://pharmacos.eudra.org/F2/eudralex/vol-2/A/pdfs-en/chap2rev1_102000.pdf (last visited Feb. 15, 2005) [hereinafter European Commission, Vol. 2A.2].

[197] Art. 3.1. of Council Regulation 2309/93.

[198] *See* European Commission, Vol. 2A.1, *supra* note 180, at 5-6; European Commission, Vol. 2A.2., *supra* note 196, at 1.

[199] Countries that have opted for the ten-year maximum period of protection cannot introduce a patent cap. COOK, *supra* note 180, at 18.

[200] According to Trevor Cook, "The 'not-beyond patent expiry' provision . . . was a qualification made at the very end of the legislative process, with all the hallmarks of a last minute political compromise." *Id*. at 43.

[201] Dodds-Smith, *supra* note 73, at 113.

[202] *But see*, as regards Spain, Segura, *supra* note 186.

[203] Trevor Cook acknowledges that the present situation is unsatisfactory. *See* COOK, *supra* note 180, at 43. He considers—in this author's opinion, erroneously—that the solution (i.e., a total prohibition of linkage) is dictated by Art. 39.3 of TRIPS.

[204] Art. 10.1(a)(iii), third sentence, of Directive 2001/83/EC.

dard is loosely applied, however; any country can claim to be acting in the interest of public health, even if its ultimate motivation is the (economic) interest of its domestic pharmaceutical industry. In other words, the European authorities do not verify whether this "public interest" condition is objectively met. The Member States currently applying this solution are Belgium, Germany, France, Italy, The Netherlands, Sweden, the United Kingdom, and Luxembourg.[205]

2. *The Abridged Application*

The scope of data protection is framed in terms of when a second applicant can rely on the original data submitted by the pioneer/first applicant. Second applicants are entitled only to an abridged marketing authorization in the specific E.U. countries where the relevant period of data exclusivity has expired.[206] The practical consequence of this rule is mitigated, however, by parallel imports, given that the European Union liberally allows brand-name drugs to be imported from low-price countries to high-price countries.[207]

According to current terminology, a second applicant can rely on the pioneer data if its drug "is essentially similar to" the pioneer/reference product. This is the "classic" generic application. The "essentially similar" requirement is deemed met if four conditions are cumulatively satisfied: 1) the generic drug has the same active ingredient in the same qualitative and quantitative composition as the reference product; 2) the generic drug has the same pharmaceutical form as the reference product; 3) the generic drug is bioequivalent to the reference product; and 4) there is no scientific evidence that the generic drug differs from the reference product with respect to safety and efficacy.[208] The first condition admits the use of different excipients by the generic manufacturer; the ECJ recently ruled that different salts of the same active principle also may constitute admissible differences.[209] With respect to the second condition, the European Com-

[205] *See* European Commission, Vol. 2A.1., *supra* note 180, at 14.

[206] *See id*. The Directive 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. On this issue, see Kingham & Castle, *supra* note 37, at 218-19.

[207] *See, e.g.,* Case C-104/75, Judgment of the Court of 20 May 1976, Adriaan de Peijper, 1976 E.C.R. I-613, *at* http://europa.eu.int/smartapi/cgi/sga_doc?smartapi!celexplus!prod!CELEXnumdoc&lg=en&numdoc=61975J0104 (last visited Feb. 15, 2005); Case C-201/94, Judgment of the Court of 12 Nov. 1996, The Queen v. The Medicines Control Agency, at 1996 E.C.R. I-5819, *at* http://europa.eu.int/smartapi/cgi/sga_doc?smartapi!celexplus!prod!CELEXnumdoc&lg=en&numdoc=61994J0201 (last visited Feb. 15, 2005); Case C-94/98, Judgment of the Court of 16 Dec. 1999, The Queen v. The Licensing Authority, 1999 E.C.R. I-8789, *at* http://europa.eu.int/smartapi/cgi/sga_doc?smartapi!celexplus!prod!CELEXnumdoc&lg=en&numdoc=61998J0094 (last visited Feb. 15, 2005); Case C-172/00, Judgment of the Court of 10 Sept. 2002, Ferring v. Eurim-Pharm, 2002 E.C.R. I-6891, *at* http://europa.eu.int/smartapi/cgi/sga_doc?smartapi!celexplus!prod!CELEXnumdoc&lg=en&numdoc=62000J0172 (last visited Feb. 15, 2005).

[208] *See, e.g.,* European Commission, Vol. 2A.1., *supra* note 180, at 12. *See also* Case C-368/96, Judgment of the Court of 3 Dec. 1998, The Queen v. The Licensing Authority (established by the Medicines Act 1968), *ex parte* Generics (UK) Ltd., The Wellcome Foundation Ltd., Glaxo Operations UK Ltd., and others, 1998 E.C.R. I-7967, ¶¶ 36, *at* http://europa.eu.int/smartapi/cgi/sga_doc?smartapi!celexplus!prod!CELEXnumdoc&lg=en&numdoc=61996J0368 (last visited Feb. 15, 2005); Case C-106/01, Judgment of the Court of 29 Apr. 2004, The Queen v. The Licensing Authority (established by the Medicines Act 1968), Novartis (UK) Ltd., 2004 E.C.R., ¶¶ 28, *at* http://europa.eu.int/smartapi/cgi/sga_doc?smartapi!celexplus!prod!CELEXnumdoc&lg=en&numdoc=62001J0106 (last visited Feb. 24, 2005); Case C-36/03, Judgment of the Court of 9 Dec. 2004, The Queen v. The Licensing Authority, Approved Prescription Services Ltd. v. Eli Lilly & Co. Ltd., *at* http://europa.eu.int/smartapi/cgi/sga_doc?smartapi!celexplus!prod!CELEXnumdoc&lg=en&numdoc=62003J0036 (last visited Feb. 24, 2005).

[209] Case C-74/03, Judgment of the Court of 20 Jan. 2005, SmithKline Beecham plc v. Laegemiddelstyrelsen, ¶¶ 31-44, *at* http://pharmacos.eudra.org/F2/pharmacos/docs/Doc2005/02_05/C-74-03%20judgment%2020%2001%202005.pdf (last visited Feb. 15, 2005). The second entrant—using either the classic abridged procedure or the hybrid procedure—may need to provided additional data to establish that the two products are still essentially similar. This need will arise if "for reasons specifically identified, [the difference in salt] must be regarded as significant as regards the safety or efficacy of the product." *Id*, at ¶¶ 39.

mission has indicated that "all oral solid pharmaceutical forms for immediate release (e.g., tablets and capsules)" constitute one same pharmaceutical form.[210]

Aside from generic drugs, a second applicant also can rely on the pioneer's data in two other circumstances. One relates to a new combination of the two previously-approved pioneer drugs.[211] In that case, the second applicant wishing to market the combination product can rely on the data pertaining to the two pioneer drugs (i.e., the individual constituents), but must provide its own data regarding the safety and efficacy of the combination. The other circumstance in which a second applicant can partly rely on the pioneer's data is when it plans to sell the active principle as the reference product, but with some added changes so that the two products are no longer essentially similar (e.g., different therapeutic indication).[212] In this case, too, the second applicant must provide its own evidence in support of the modifications brought to the reference product. In both circumstances, the Directive basically confirms what is only logical: if there are no pre-existing data supporting all of the novel aspects of the second applicant's drug, then the latter must supply the necessary evidence.

3. *The Notion of Reliance*

The European Union 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. 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.[213] Its application is referred to as an "informed consent" abridged application.[214]

As in the United States, a second applicant can still rely on data pertaining to a reference product that was withdrawn, provided that the reason for the withdrawal was not related to safety or efficacy (e.g., a purely commercial reason).[215] A 2003 decision of the European Court of Justice (ECJ), however, insisted that the reference product's marketing authorization be in force at the time the generic applicant filed its abridged application.[216] The result of this decision is that the innovator company can block the

[210] *Id*. at 13. *See also* the Novartis case C-106/01, *supra* note 208, ¶¶ 37-42. Under the revised Directive 2001/83/EC, the new Art.10.2.(b) confirms this.

[211] *See* Art. 10.1.(b) of Directive 2001/83/EC; European Commission, Vol. 2A.1., *supra* note 180, at 15. As for the revised version of Directive 2001/83/EC, see its Art. 10b.

[212] This application under the proviso of Art. 10.1.(a)(iii), second para. of Directive 2001/83/EC (corresponding to Article 10.3 of the revised Directive) sets forth the hybrid application. *See also* ECJ Case C-106/01, *supra* note 208, ¶¶ 49-55; ECJ Case C-74/03, *supra* note 209, ¶¶ 24-25; European Commission, Vol. 2A.1., *supra* note 180, at 15. C*ompare* with a section 505(b)(2) NDA in the United States.

[213] Art. 10.1.(a)(i) of Directive 2001/83/EC. Under the revised version of Directive 2001/83/EC, see its Art. 10c.

[214] *See* European Commission, Vol. 2A.1., *supra* note 180, at 6, 10, 13.

[215] *Id*. at 11. Hence,

> If a marketing authorization holder of an original medicinal product asks for the withdrawal of an authorization in favour of an authorization for a medicinal product of which the composition in active substances, the strength and the pharmaceutical form are the same but which differs regarding excipients while maintaining the same efficacy and safety, both formulations can be a reference for an application for an essentially similar medicinal product.

Id. at 11.

[216] Case C-223/01, Judgment of the European Court of Justice of 16 Oct. 2003, in AstraZeneca v. Generics (UK) Ltd., 2003 E.C.R. I-11809, at ¶¶ 42-54, *at* http://europa.eu.int/smartapi/cgi/sga_doc?smartapi!celexplus!prod!CELEXnumdoc&lg=en&numdoc=62001J0223 (last visited Feb. 15, 2005). *See also* European Commission, Vol. 2A.1., *supra* note 180, at 11.

entry of generic competitors by replacing an "old" drug with a newer version (e.g., a tablet instead of a capsule) and obtaining the withdrawal of the marketing authorization covering the "old" version before the generic applicant lodges its application. Obviously, this result does not promote generic competition.

The above-mentioned ECJ decision further clarified two other aspects of current data exclusivity. First, subject to the exception just reviewed, if the reference product's marketing authorization is national (i.e., delivered following either a purely national or a mutual recognition procedure), it must be in force in the Member State where the generic manufacturer files its application;[217] if this is not the case, the generic applicant cannot receive approval in that Member State. The continued availability of the reference product in other Member States is of no assistance. This ruling, adverse to the interest of the generic industry, has also been rectified by the revised version of Directive 2001/83/EC.[218] Second, the ECJ found that it is sufficient that the marketing authorization be in force in the relevant Member State, even if the product actually has not been marketed in that State.[219] The revised Directive maintains this rule.[220]

According to Part II.2 of Annex I to Directive 2001/83/EC,[221] a generic applicant normally can use the abridged procedure to market a different salt, ester, or derivative of the reference product's active substance.[222] The generic manufacturer may have to prove that this change has no bearing on the safety and efficacy of its generic drug, particularly with respect to the pharmacokinetics, pharmacodynamics, and toxicity of the moiety.[223] This rule is further buttressed by Article 10.2.(b) of the revised Directive 2001/83/EC.

4. *Substantive Requirements*

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 state any other specific requirements; in particular, it does not specify whether the product has to be an entirely new chemical entity never before approved.

5. *Additional Exclusivity for Line Extensions?*

Contrary to U.S. law, current E.U. data exclusivity does *not* grant additional periods of protection for subsequent improvements brought to a drug (under the revised Directive see subchapter IV.C.3.b *infra*). Variations (i.e., modifications) brought to the pioneer product (e.g., new therapeutic indications) are not given any protection. Once the one

[217] If the reference product's authorization was delivered through the centralized procedure, the authorization is in force in all E.U. countries. The generic applicant must then follow the centralized procedure, too. *See* European Commission, Vol. 2A.1., *supra* note 180, at 11.

[218] *See* Art. 10.1, first and third subparas. of revised Directive 2001/83/EC.

[219] *See* Case C-223/01, *supra* note 216, ¶¶ 25-29.

[220] *See* Art.10.1, first subpara. of revised Directive 2001/83/EC.

[221] Member States had until October 31, 2003, to implement Directive 2003/63/EC, amending Directive 2001/83/EC.

[222] *See* Part II, points 2 and 3 of the new Annex I to Directive 2001/83/EC. *See also* Medicines and Healthcare Products Regulatory Agency (MHRA), Notification of Change of Policy with Respect to Products Containing Different Salt or Ester Forms of the Active Moiety Compared to the Original Product (Aug. 26, 2003), *at* http://www.mhra.gov.uk/news/2003/saltesterpolicy_260803.pdf (last visited Feb. 15, 2005); European Commission, Vol. 2A.1., *supra* note 180, at 12.

[223] *See* European Commission, Vol. 2A.1., *supra* note 180, at 12, 24. The abridged procedure is no longer available if the use of a different salt, ester, or derivative entails a difference in safety or efficacy.

period of exclusivity expires, second applicants can rely upon any data "added" to the file, even though that added portion of data has not benefited from a full six-to-ten-year-period of exclusivity.

This harsh result is not immediately apparent from the Directive's language, but stems from a 1998 ECJ reading of the Directive.[224] The court reasoned that a second applicant's reliance on the pioneer's data is possible only if the two drugs are "essentially similar."[225] Then, the court interpreted the words "essentially similar" as meaning that the two drugs must have "the same qualitative and quantitative composition in terms of active principles and the same pharmaceutical form"[226]—a definition that entirely disregards the use to which the drug is put.[227] In other words, if a brand-name company markets two versions of its drug for two different indications, these two versions are considered to constitute one product as long as they have the same active ingredient. The court reached this decision despite the European Commission's pleadings that at least innovative new therapeutic indications ought to be protected.[228] The ECJ held that this innovation criteria would not be precise enough to guarantee legal certainty.[229] As a result, a second applicant can rely on the pioneer's data to market a generic drug directed for all therapeutic indications approved for the pioneer drug. What is true of new therapeutic indications also is valid for new "dosage forms, doses and dosage schedules."[230] Thus, the second applicant can—after the expiry of the initial data protection period and relevant patents—sell copies of all approved versions of the pioneer drug. This position has been confirmed in other recent cases, notably for line extensions introduced by the pioneer company involving different routes of administration, different pharmaceutical forms, different doses or different bioavailability.[231]

The 1998 ECJ decision was good news for the generic industry, and a major setback for the research-based industry.[232] Yet, the legal reasoning of the court is exceedingly abrupt.[233] If the court had focused on the words "product … authorized … in accord with Community provisions in force …" (instead of focusing on the "essentially similar" language), it might have reached a different conclusion. The question would then have

[224] Case C-368/96, *supra* note 208. *See also* Dodds-Smith, *supra* note 73, at 121, 123.

[225] Case C-368/96, *supra* note 208, ¶¶ 20-37.

[226] The Court's precise definition is the following:

> a medicinal product is essentially similar to an original 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.

Case C-368/96, *supra* note 208, conclusion 1. *See also* European Commission, Vol. 2A.1., *supra* note 180, at 12.

[227] *See* Case C-368/96, *supra* note 208, ¶ 42.

[228] *See id*. ¶¶ 45-46. The Commission referred, in particular, to major changes that require the filing of a new marketing application as per Annex II of Commission Regulation (EC) No. 541/95 of 10 March 1995 concerning the examination of variations to the terms of a marketing authorization granted by a competent authority of a Member State, O.J. 1995 (L 55) at 7, *at* http://pharmacos.eudra.org/F2/eudralex/vol-5/pdfs-en/950541en.pdf (last visited Feb. 15, 2005).

[229] *See* Case C-368/96, *supra* note 208, ¶ 48.

[230] *Id*. ¶ 56.

[231] *See* Case C-106/01, *supra* note 208, ¶¶ 58-66; Case C-36/03, *supra* note 208, ¶¶ 21-30.

[232] One law firm even called it a "decisive defeat." *See* Fish & Richardson, *Landmark Decision on Non-Patent Marketing Exclusivity for Pharmaceutical Products in European Union Will Significantly Impact Generic and Research-Based Industries* (Dec. 1998), *at* www.fr.com/practice/landmark.cfm (last visited Feb. 15, 2005).

[233] According to Dodds-Smith, the court "did not address the arguments and counter-arguments in any depth and there was virtually no discussion of the specific rationale for Directive 87/21." *See* Dodds-Smith, *supra* note 73, at 127, 131-32.

centered on how to define the words "authorized product." The court would have inquired, for example, whether a new authorization for a new indication is held to give rise to a "new product;" had that answer been affirmative, this new product would have been entitled to an independent period of protection.

A similar critique can be directed against the other arguments decided by the ECJ. The innovator company claimed that the interpretation outlined above violated the principles of protection of innovation, nondiscrimination, proportionality, and respect for property.[234] The court flatly rejected these claims, each time with little more than a paragraph. For example, it found that the nondiscrimination principle was obeyed, in essence, because the first and second applicants were not in the same position, given that the latter can rely on the former's data.[235] It is regrettable that the ECJ was so cursory in its analysis, because some of the issues raised by the parties are interesting even beyond the scope of the European system. In particular, the claim that the principle of respect for the right of property is infringed corresponds to an issue that has arisen with respect to the U.S. Constitution's "Takings Clause."[236] The European court barely addressed that claim, saying that "the right to property may be restricted, provided that the restrictions in fact correspond to objectives of general interest pursued by the Community and do not constitute disproportionate and unacceptable interference impairing the very substance of the right guaranteed"[237]—conditions "robotically"[238] found to have been met in the present case. Ian Dodds-Smith suggests that the ECJ may have been "frustrated by the limited assistance given to it by the text of the Directive and balked at the extensive rewriting that would be required in order to strike a better balance between competing interests."[239]

Another important question is how to reconcile this court's decision with Article 10.1(a)(iii), which apparently extends ten-years of protection to *all* medicinal products approved though the centralized procedure. Part B of Appendix I to the Council Regulation (EEC) 2309/93 allows certain drugs that do not contain a new active substance to follow the centralized procedure. For example, "[m]edicinal products presented for an entirely new indication which, in the opinion of the agency, is of significant therapeutic interest" are eligible for approval by the EMEA. In those cases, there are no new active ingredients or NCEs; there are only new indications. The question, therefore, is whether the court's general interpretation should prevail over the apparently unequivocal language of the Directive. Given that the ECJ centered its analysis on the words "essentially similar to," its general opinion is not limited to products approved through the mutual recognition procedure.[240] Therefore, new drug uses approved through the centralized procedure currently should not receive extra protection. The position of the EMEA however appears to be more nuanced.[241]

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[234] *See* Case C-368/96, *supra* note 208, ¶ 60.

[235] *See id.* ¶ 63.

[236] *See, e.g.,* Ruckleshaus v. Monsanto Co., 467 U.S. 986 (1984); Tri-Bio Labs., Inc. v. United States, 836 F.2d 135 (3d Cir. 1987). The first case involved an application for a pesticide and the second one for a generic animal drug. Both were concerned with Fifth Amendment taking. See also the citizen petitions to the FDA mentioned in note 3 *supra*.

[237] *See* Case C-368/96, *supra* note 208, ¶ 79.

[238] The expression is from Fish & Richardson, *supra* note 232.

[239] Dodds-Smith, s*upra* note 73, at 129.

[240] The opposite opinion apparently was taken by Trevor Cook, as cited in Carlos Correa, *Unfair Competition Under the TRIPS Agreement: Protection of Data Submitted for the Registration of Pharmaceuticals*, 3 CHI. J. INT'L L. 69, 71 n.4 (2002). *See also* Kingham & Castle, *supra* note 37, at 221.

[241] Dr. Blattner at the EMEA wrote: "when a medicinal product has previously been approved through MRP [mutual recognition] and then goes through the centralised procedure with a full new application that includes new documentation and leads to a new centralised marketing authorisation, [it] will receive the 10 year of data protection regarding the new presented data." E-mail from Dr. Olivier Blattner, Reg. Affairs and Organisational Support, EMEA (May 12, 2004) (on file with author).

C. *The Revised 2001/83/EC Directive*

The European Union launched an important initiative in July 2001 to revise key aspects of the E.U. legislation on pharmaceuticals (2001 Pharma Review). The Pharmaceutical Review package also included changes to the regulation governing the EMA.[242] Data exclusivity was a key topic targeted for review[243] and the duration of data exclusivity was among the most contentious issues to be decided.[244]

1. *Position of the Research-Based Pharmaceutical Industry*

With the support of the European Commission,[245] the brand-name industry aimed to harmonize periods of data protection upwards: it sought to replace the six-year minimum period with a uniform ten-year period.[246] The innovative industry argued that different periods of protection generate "confusion and uncertainty."[247] It further claimed that longer periods of exclusivity represent fair compensation for the lack of freedom to price drugs in Europe.[248] The European Commission also proposed to remove the link between data exclusivity and patent protection, thus preventing countries from capping the period of data exclusivity once the patent expires.[249]

The European brand-name pharmaceutical industry also lobbied to extend data exclusivity to secondary uses or other variations brought to an initial marketing authorization.[250] It

[242] The regulation modified was Regulation No.2309/93 laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products, OJ *L 214, 24/8/1993, at 1, at* http://pharmacos.eudra.org/F2/eudralex/vol-1/REG_1993_2309/REG_1993_2309_EN.pdf (last visited Feb. 24, 2005). It was replaced by Regulation 726/2004, *supra* note 192. Furthermore, the Community code on veterinary product and the Directive on herbal medicinal products were also changed; they are of no relevance here.

[243] *See* Appendix I to this article.

[244] *See infra* discussion in Part IV.D.3.

[245] *See, e.g.,* Reform of EU Pharmaceutical Legislation 5 (MEMO/01/267) (July 18, 2001), *at* http://pharmacos.eudra.org/F2/review/doc/brief_m01_267_en.pdf (last visited Feb. 15, 2005); European Commission Proposal for One Regulation and Two Directives Pertaining to Medicinal Products 404 (COM(2001)) (Nov. 26, 2001), *at* http://europa.eu.int/eur-lex/en/com/pdf/2001/en_501PC0404_01.pdf (last visited Feb. 15, 2005) [hereinafter European Commission 2001 Proposal]. The European Union had the support of the United States, which also favored upward harmonization. *See* TransAtlantic Business Dialogue, Extract of Charlotte Statement of Conclusions Re: Pharmaceutical Sector, *at* http://pharmacos.eudra.org/F2/pharmacos/docs/TABDCharlotte1.pdf (last visited Feb. 15, 2005).

[246] *See, e.g.,* Eli Lilly's response to the G-10 Medicines Group Secretariat 3 Nov. 21, 2001), *at* http://pharmacos.eudra.org/F3/g10/docs/responses/resp2/17.pdf (last visited Feb. 15, 2005); Boots HealthCare Int'l, Response to the Consultation Paper by the High Level Group on Innovation and the Provision of Medicines 2, *at* http://pharmacos.eudra.org/F3/g10/docs/responses/5.pdf (last visited Feb. 15, 2005).

[247] Kingham & Castle, *supra* note 37, at 223.

[248] *See* G10 Workshop on Generic Medicines**,** Summary at 1-2 (Dec. 7, 2001), *at* http://pharmacos.eudra.org/F3/g10/docs/w_generics.pdf (last visited Feb. 15, 2005). *See also* verbatim report of Parliamentary proceedings, position of Erkki Liikanen, European Commissioner (Dec.16, 2003) *at* http://www2.europarl.eu.int/omk/sipade2?L=EN&PUBREF=-//EP//TEXT+CRE+20031216+ITEM-006+DOC+XML+V0//EN&LEVEL=3&NAV=X (last visited Mar. 31, 2004) ("Somebody referred to the situation in America where exclusivity periods are shorter. Compare the costs for a moment. Because we in Europe cover the costs from public budgets we want to have a say in pricing levels. The longer protection period gives some compensation for innovation, due to the lower prices.").

[249] European Commission 2001 Proposal, *supra* note 245, at 72 n.7. *See also supra* discussion Part IV.B.1.c.

[250] Cameron McKenna and Andersen Consulting surveyed the participants in the European drug approval process and found that the research-based industry was overwhelmingly in favor of an upward harmonization of periods of data protection. CAMERON MCKENNA (CMS) & ANDERSEN CONSULTING, EVALUATION OF THE OPERATION OF COMMUNITY PROCEDURES FOR THE AUTHORISATION OF MEDICINAL PRODUCTS 41-42, 182-87 (2000), *at* http://pharmacos.eudra.org/F2/pharmacos/docs/Doc2000/nov/reportmk.pdf (last visited Feb. 15, 2005).

appealed to the three-year exclusivity offered in the United States.[251] A trade-off between longer and broader exclusivity periods and a *Bolar* clause was put on the negotiation table.[252]

2. *Position of the Generic Industry*

Predictably, the proposals described above provoked the opposition of the European generic industry,[253] which proposed instead to harmonize all E.U. protection periods downward to the U.S. benchmark of five years.[254] Invoking the 1998 ECJ decision discussed above, the generic industry rejected any period of protection for new therapeutic uses as well as for line extensions. It vehemently opposed the trade-off between data exclusivity and a *Bolar* clause; in its opinion, the lack of a *Bolar* clause did not prevent European generic manufacturers from performing the necessary testing of their generic products, but obliged them only to move this testing abroad (i.e., outside the European Union).[255] Adding a European *Bolar* provision merely provides the impetus for bringing back within the European Union jobs that deliberately were created outside the Union; this would benefit the entire economy, without conferring special advantages to the European generic industry.

The ten countries to accede to the European Union in May 2004 also expressed their opposition to lengthening the periods of data protection.[256] They feared that longer periods would negatively impact their healthcare budgets, given that generic drugs represent the majority of drugs consumed.

3. *Solutions Implemented*

Because of the lack of consensus between the two aforementioned groups,[257] the adoption of the revised Directive 2001/83/EC entailed lengthy negotiations among the

[251] "It is, quite simply, inexplicable that EC law makes no clear provision to protect the research investments required to discover such indications and prove their safety and efficacy to regulators." Kingham & Castle, *supra* note 37, at 223.

[252] *Bolar* clauses allow generic manufacturers to use the patented drug to conduct their bioequivalence testing and other studies necessary to secure marketing approval immediately after the patent on the pioneer drug expires. The name "Bolar" comes from a decision of the U.S. Court of Appeal for the Federal Circuit, which found that generic manufacturers were infringing pioneer drug patents when they used the latter to prepare their ANDAs. *See* Roche Prods. v. Bolar Pharm. Co., 733 F.2d 858 (Fed. Cir. 1984), *cert. denied,* 469 U.S. 856 (1984). The 1984 Hatch-Waxman Act reversed this decision. On the American *Bolar* exemption, see also Gregory N. Pate, *Analysis of the Experimental Use Exception*, 3 N.C. J.L. & TECH. 253 (2002). Also Engelberg, *supra* note 16, at 399 (explaining that, at the beginning of the negotiations surrounding the Hatch-Waxman Act, the brand-name pharmaceutical industry and the generic industry were relying on the district court opinion that had conceded a *Bolar* experimental use exemption to patent infringement).

[253] The generic industry developed additional arguments along the line described in subpt. II.A., *supra*.

[254] *See* EGA, BREAKTHROUGH 2001, GENERIC MEDICINES AND EU PHARMACEUTICAL LAW, ch. 4.2., *at* http://www.pharmalaw.org/EGA%20documents%20(pdf)2.pdf (last visited Feb. 24, 2005).

[255] *See* EGA, GENERIC MEDICINES AND THE EUROPEAN COMMISSION'S PROPOSALS FOR AMENDING PHARMACEUTICAL LAW (Sept. 14, 2001); Press Release, EGA, Bolar for 11 Years Data Exclusivity—A False Trade Off (July 16, 2001), *both documents available at* http://www.pharmalaw.org/EGA%20documents%20(pdf)2.pdf (last visited Feb. 24, 2005). *See however* EGA, EGA BOARD OF DIRECTORS URGES EARLY IMPLEMENTATION OF "EU BOLAR PROVISION" FOR GENERICS TO ENSURE THE FUTURE OF EUROPEAN RESEARCH & DEVELOPMENT (Mar.25, 2004), *at* http://www.egagenerics.com/pr-2004-03-25.htm.

[256] Acceding Countries' Declaration of Milan of 5 Sept. 5, 2003, signed by the Ministers of Health, *at* http://www.egagenerics.com/doc/milandec.pdf (last visited Feb. 24, 2005). The ten countries are Cyprus, Czechoslovakia, Estonia, Hungary, Latvia, Lithuania, Malta, Poland, Slovakia, and Slovenia. *See also* Press Release, EGA, EU Pharmaceutical Law Threatens Access to Medicines in Central and Eastern Europe (July 8, 2003), *at* http://www.egagenerics.com/pr-2003-07-08.htm (last visited Feb. 24, 2005).

[257] "Finally, there was very strong support for harmonising the periods of data protection, but less consensus on what the harmonised level of protection should be or how it should be applied to products derived from incremental research." European Commission 2001 Proposal, *supra* note 245, at 75, 133.

European Parliament, the Commission, and the Council.[258] A "compromise package" finally was agreed upon in December 2003. The revised Directive was published in the *Official Journal* (*O.J.*) on April 30, 2004.[259] Member States have until October 30, 2005 to implement it (hereinafter "implementation date").[260] As alluded to in subpart IV.A. *supra*, the new data protection periods will benefit only drugs which are submitted for authorization after the implementation date of the revised Directive (nonretroactivity rule).[261] Drugs approved before that date remain subject to the 6/10 system.[262] Therefore, most abridged applications to be filed in the next ten years or so will be based on the 6/10 system.

Given the significant differences between the two versions of the Directive, the nonretroactivity rule may give rise to legal and practical difficulties during the interim period. For example, according to the revised version, a generic application can be filed even if the pioneer company, by that time, has, withdrawn the reference product (for nonsafety reasons). According to a 2003 ECJ decision,[263] however, a generic application must be filed (although not necessarily approved) at a time when the reference product is still marketed.[264] Should this decision continue to be applied to products approved before the implementation date? The answer is probably yes, but deserves to be addressed- probably in an updated Notice to Applicants.

a. *New Drugs*

The revised Directive introduces the "8+2+1" formula for new drugs,[265] approved either through the centralized procedure or the mutual recognition procedure.[266] More

[258] *See, e.g., European Revisions Offer New Freedoms for Generics*, GENERICS BULLETIN (Bus. Newsletter for the Generic Med. Indus.), Jan. 16, 2004, at 18, *at* http://www.egagenerics.com/doc/PhRev_GB-2004-01-16.pdf (last visited Feb. 24, 2005) [hereinafter 2004 GENERICS BULLETIN]; Brian Ager, Director General of the EFPIA, Review of the EU Pharmaceutical Legislation: EFPIA Comment on Outcome of EP Final Vote (Second Reading) (Jan. 2004), *at* http://www.efpia.org/3_press/FMLBAJan%202004.pdf (last visited Feb. 15, 2005). *See also* Appendix I to this paper (summarizing the various steps that led to the adoption of the revised Directive 2001/83/EC).

[259] *See* 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, OJ L 136/34, 30.4.2004, *at* http://europa.eu.int/eur-lex/pri/en/oj/dat/2004/l_136/l_13620040430en00340057.pdf (last visited Feb. 24, 2005). The consolidated text is available at http://pharmacos.eudra.org/F2/eudralex/vol-1/CONSOL_2004/Human%20Code.pdf (last visited Feb. 24, 2005)..

[260] *See* Arts.3 and 4 of the revised Directive 2001/83/EC. Acceding Member States can make requests for longer transitional periods. *See* Speech of Erkki Liikanen (member of the European Commission responsible for enterprise and the Information Society) (SPEECH/03/615), Strasbourg (Dec.16, 2003), *at* http://pharmacos.eudra.org/F2/pharmacos/docs/Doc2003/dec/speech_3_615_en.pdf (last visited Feb. 15, 2005).

[261] *See* Art.2 and 3 of the revised Directive 2001/83/EC. In the words of the EFPIA,

> Assuming the Future medicines Legislation is finalized in 2004 and implemented in early 2006, its data protection provisions will have no impact on the availability of generic drugs in the enlarged EU until 2012 (for countries with 6 years data protection under the current legislation), or until 2016 (for countries with 10 years data protection under the current legislation).

EFPIA, Future Medicines Legislation, Impact on the Accession Countries of the "Regulatory Data Protection" Provisions in the Council Common Position (Nov. 2003), *at* http://www.efpia.org/3_press/FMLfacts.pdf (last visited Feb. 15, 2005) *See also* EGA, Data Exclusivity and Market Protection, *supra* note 73.

[262] *See, e.g.,* Speech of Erkki Liikanen, *supra* note 260.

[263] *See* Case C-223/01, *supra* note 216.

[264] *See supra* subpt. IV.B.3.

[265] Art. 10.1 of revised Directive 2001/83/EC.

[266] The previously-existing distinction between high-technology medicinal products and other products is thus removed. *See supra* subpt. IV.B.1.a.

specifically, data exclusivity lasts eight years (starting with the initial approval of the reference medicinal product),[267] but the second applicant cannot place its drug on the market before ten years have elapsed (starting from this same date).[268] Therefore, the second applicant can file its request for a (generic) marketing authorization after eight years, but has to wait two more years before the authorization is made effective.[269] At that point, the second entrant can sell its drug in all Member States, even those where the reference medicinal product is not—or is no longer—marketed.[270]

A *Bolar* provision eventually has been added, allowing generic manufacturers to engage (in the European Union) in testing and preregistration activities even if the patent protecting the reference drug is still ongoing.[271]

b. *New Uses of New Drugs*

According to the revised Directive, drugs for which a new use (i.e., therapeutic indication) has been approved receive an additional one-year protection period.[272] Other changes are *not* rewarded by this one-year protection period. Hence, there is (still) no data protection period for new strengths, new pharmaceutical forms, new administration routes, or new presentations. All of these variations are said to belong to the same global authorization.[273]

For a drug whose original presentation received the "8+2" protection period, the application for the new therapeutic indication use must be made during the first eight years (following the initial authorization). Additionally, the new use must "bring significant clinical benefit in comparison with existing therapies."[274] The drug agency decides whether this condition is met. Guidance should further explain what is meant by "significant clinical benefit."

Only a single one-year period is allowed: accumulating several one-year periods for successive newly-discovered uses is not allowed.[275] The one-year period covers both the new use and the "old" ones, so a generic applicant cannot market a drug labeled for the "old" therapeutic indications during this period.[276]

c. *New Uses of Old Drugs*

"Well-established" products are entitled to receive a one-year data protection period if they are granted approval for a new therapeutic indication.[277] 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.[278] This one-year period protects only the new use, and not the "old" ones. It can be obtained only once.

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[267] Art. 10.1, first subpara. of revised Directive 2001/83/EC.

[268] Art. 10.1, second subpara. of revised Directive 2001/83/EC.

[269] This additional two-year period is sometimes referred to as "market exclusivity," in opposition to the eight-year period of "data exclusivity." *See* 2004 GENERICS BULLETIN, *supra* note 258, at 19.

[270] Art. 10.1, third subpara. of revised Directive 2001/83/EC.

[271] Art. 10.6 of revised Directive 2001/83/EC.

[272] Art. 10.1, fourth subpara. of revised Directive 2001/83/EC.

[273] *See* Art. 6.1 of revised Directive 2001/83/EC.

[274] *Id*.

[275] *Id*.

[276] *See* 2004 GENERICS BULLETIN, *supra* note 258, at 20. Compare with the United States; *see supra* discussion in Part III.C.5.

[277] Art. 10.5 of revised Directive 2001/83/EC.

[278] *Id*.

d. *Rx to OTC Switches*

Pursuant to Article 74a of the revised Directive, prescription (Rx) to over-the counter (OTC) switches (i.e., a change of classification from Rx-only to OTC) are entitled to a one-year data protection period, provided that the change was authorized on the basis of "significant preclinical tests or clinical trials." Not all switches require prior testing; in most circumstances, there already is enough information regarding the safety profile of the drug at the time of switching. If tests are nonetheless necessary, and if the corresponding exclusivity is granted, a second entrant cannot request that its generic drug be switched to OTC status; it can continue, however, to sell its copy as a prescription drug.

e. *Generic Biopharmaceuticals*

Finally, the revised 2001/83/EC Directive envisions the approval of generic biopharmaceuticals (called "biosimilar medicinal products" in Europe).[279] At least theoretically, it acknowledges that manufacturers of biosimilar medicinal products, in some circumstances, can follow an abridged procedure.[280] This change potentially holds great significance because the admissibility of generic biopharmaceuticals has been immensely controversial both in Europe and in the United States.[281] The European trade association for the biotechnology industry fought vigorously against this possibility of admitting generic biopharmaceuticals.[282] Unfortunately, the relevant language of the revised Directive regarding biosimilar products is vague—perhaps intentionally so. It calls for further clarification through guidelines.[283] In November 2004, the EMA set forth the general framework for biosimilar medicinal products in a new guideline.[284]

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[279] *See* Art. 10.4 of Revised Directive 2001/83/EC. The more stringent approach proposed by the European biotechnology trade group, EuropaBio, was not retained. *See* EuropaBio, Position on Biosimilar Medicinal Products as Regulated in the Common Position on the Revision of Directive 2001/83/EC on the Community Code for Human Medicines (Oct. 1, 2003), *at* http://www.europabio.org/positions/posbiosimilar.doc (last visited Feb. 24, 2005).

[280] In most cases, however, it is contemplated that an applicant wishing to sell a copy of a pioneer biopharmaceutical will need to provide preclinical and/or clinical data. *See* EMA, Committee for Medicinal Products for Human Use (CHMP), Draft Guideline on Similar Biological Medicinal Products (CHMP/437/04), (Nov.16, 2004), http://www.emea.eu.int/pdfs/human/biosimilar/043704en.pdf [hereinafter CHMP Draft 2004 Guideline]. *See also* EuropaBio, Position on Biosimilar Medicinal Products, *supra* note 283.

> Where a company claims similarity with another marketed product,
> [It] may not be necessary to repeat all safety and efficacy studies if the applicant can demonstrate that 1) it is possible to characterize the product in detail with respect to physico-chemical properties and *in vitro* activity, and 2) comparability can be shown from a chemical-pharmaceutical perspective.

Id. at 8.

[281] *See, e.g.,* Biotechnology Industry Organization, BIO Citizen Petition to the FDA, Follow-on Therapeutic Proteins (Apr. 23, 2003), *at* http://www.bio.org/healthcare/pharmaceutical/BIO_CP—FINAL_DRAFT_4_22_03.pdf (last visited Feb. 24, 2005).

[282] *See, e.g.,* EuropaBio, Biologics and Biosimilar Products: Frequently Asked Questions (Sept. 15, 2003), *at* http://www.europabio.org/documents/QA-biosimilar.doc (last visited Feb. 24, 2005). *See also* the slightly more detailed analysis proposed by PHRMA, ISSUES AND QUESTIONS ON BIOLOGICS, *supra* note 36, at 2-9.

[283] *See, e.g.,* Press Release, EuropaBio, Europe Is First to Rule for Biosimilar Products (Dec. 17, 2003), *at* http://www.europabio.org/articles/article_271_EN.doc (last visited Feb. 24, 2005); EGA, Precise and Rapid Implementation of New EU Pharmaceutical Legislation Is "Top of the Agenda" for EGA Regulatory Affairs Conference (Feb. 9, 2004), *at* http://www.egagenerics.com/pr-2004-02-09.htm (last visited Feb. 24, 2005).

[284] *See* CHMP Draft 2004 Guideline, *supra* note 280. Since 2003, the EMA has released several other class-specific and product-specific guidelines (see the documents available from http://www.emea.eu.int/htms/human/biosimilar/biosimilarcon.htm).

V. CONCLUSION AND RECOMMENDATIONS

This conclusion reviews five principal objections against the present system of marketing/data exclusivity and suggests possible improvements.

A first criticism relates to the excessively broad scope of marketing exclusivity. While its main goal is to encourage valuable research by allowing the sponsor to recoup its initial investment, the system tolerates unwarranted benefits. For instance, the sponsor may have fully recouped its investment long before the exclusivity has expired. Alternatively, the investment may have been so small to begin with that it does not warrant exclusivity. Moreover, the sponsor may have invested in the research and the product improvement even without exclusivity. An innovator company can benefit by extending its product line even if—or sometimes, because—it faces generic competition (e.g., to promote brand loyalty).[285] To account for these limitations of the existing system, it has been proposed to sunset exclusivity provisions once the exclusivity holder has recouped a multiple of its investment or has reached a set level of income or profits.[286] Others advocate for more transparency in the R&D cost structure: pharmaceutical firms that want to receive marketing exclusivity should disclose their out-of-pocket expenditures. These private expenditures should be set apart from funds received from governmental entities; similarly, assistance provided by government-funded research institutions or universities should be divulged. Tax relief also should be taken into account to assess the "real" contribution of the pharmaceutical company.[287] A third remedial proposal would be to require a degree of innovation or therapeutic benefit for exclusivity to be granted. If the change incorporated into the drug is so obvious that anyone could have implemented it, even a three-year period of exclusivity may be too much of a reward. The same can be true, albeit to a lesser degree, for NCEs: it is not patent that NCEs are, by definition, innovative. The EGA, for instance, has claimed that less than half of the 126 products approved through the European centralized procedure in its first five years "could be regarded as innovative."[288]

A second and weightier criticism is that data covered by marketing exclusivity are rarely, if ever, made public.[289] While patentees receive twenty years of exclusivity in exchange for disclosing their invention, drug companies receive up to ten years of exclusivity without having to disclose their protected data. Even when that period has lapsed, the data are not made available to the public.[290] Drug agencies are sitting on hoards of precious information,[291] which would be put to better use if it were made

[285] Brand loyalty explains why many brand-name companies do not lose their entire market share after entry of generics at a lower price. *See, e.g.,* NIHCM FOUNDATION, A PRIMER: GENERIC DRUGS, PATENTS AND THE PHARMACEUTICAL MARKETPLACE 17 (June 2002), *at* http://www.nihcm.org/GenericsPrimer.pdf. (last visited Feb. 15, 2005).

[286] *See* Love Statement, Data Exclusivity, *supra* note 32.

[287] *See* EGA, MAJOR OBSTACLE, *supra* note 22, at 5.

[288] *See* EGA, Generic Medicines and Innovation, EGA Fact Sheet No. 3, *at* http://www.egagenerics.com /doc/fs_innovation.pdf (Feb. 24, 2005).

[289] Even when a drug is withdrawn for safety reasons, the complete clinical dataset unfortunately is not always made public; thus, other companies may invest in the same fruitless avenue of research. In that case, however, FDA would stop any ongoing investigational new drug applications (INDs) by other sponsors and warn the latter of the problems encountered with the "old" drug. *See also* Public Citizen Health Research Group v. FDA, 185 F.3d 898 (D.C.Cir. 1999).

[290] *See* EGA, MAJOR OBSTACLE, *supra* note 22; also EGA, New Threat to Affordability, *supra* note 5.

[291] Peter Hutt, former FDA Chief Counsel once said: "The [FDA] is the largest repository of private scientific research in the world. [It] receive[s] mountains of important data and information on the safety, effectiveness, and functionality of foods and drugs . . . ." John C. O'Qui, *Protecting Private Intellectual Property From Government Intrusion: Revisiting SmithKline and the Case for Just Compensation*, 29 PEPP. L. REV. 435, 468 (2002). The Freedom of Information Act (FOIA; 5 U.S.C. §552) makes much—but not all—of this information available to the public.

available to researchers throughout the world. Another objection related to this lack of transparency is that it hampers efforts by nongovernmental organizations (NGOs) (or other members of the public) to perform their own analysis of the risk/benefit ratio performed by the national drug agencies.[292] For instance, in the United States, Public Citizen regularly examines whether approved drugs have an acceptable risk profile, and has petitioned to have several drugs withdrawn from the market owing to excessive risks. FDA frequently heeds Public Citizen's observations. When these NGOs lack access to the raw data of clinical trials, however, they draw their conclusions from an incomplete set of information.

A third criticism is that most data protected by marketing exclusivity were generated through clinical trials. Human subjects agreed to participate in these trials to further the progress of science, without being guaranteed that they personally would profit by receiving new and better treatments. Clinical trials thrive, in large part, thanks to the altruism of volunteers. This altruism and dedication to the advancement of science are contradicted if trial sponsors (i.e., pharmaceutical companies) can forever keep the information to themselves. This leads potentially to the repetition of clinical trials already conducted.[293] The situation is particularly dire when a trial shows complete or partial failure of the treatment. Whether or not a drug finally receives approval, divulging the raw data has the potential to reduce the number and scope of future clinical studies. Additionally, better drugs could be devised by studying both the successful and unsuccessful clinical studies.

A fourth criticism of marketing exclusivity is that it encourages staged incremental amelioration to drug products. Firms have an incentive to introduce line extensions when the patent and exclusivity protections on their existing drugs are about to expire, thus stretching the total period of protection. In addition, the latter years of patent/exclusivity life are usually more valuable because the company has by then attained its greatest market share. Hence, a firm could choose to delay for years a valuable improvement to a product; only when the latter runs short on patent and exclusivity protections, will its sponsor file an NDA or supplement to trigger the new exclusivity period.

A fifth criticism is related to the lack of appeal mechanism against exclusivity determinations. Competitors cannot challenge an agency's determination that a rival drug deserves exclusivity. This is of particular concern regarding three-year exclusivity in the United States, given that it calls for specific conditions to be fulfilled. If, for example, an innovator company has not submitted a truly essential clinical study to support the requested change to its product, there is no mechanism to rescind its exclusivity.

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[292] *See, e.g.,* Margaret Witherup Tindall, *Breast Implant Information as Trade Secrets: Another Look at FOIA's Fourth Exemption*, 7 ADMIN. L.J. AMER. UNIV. 213 (1993).

[293] Teva, for instance, praised the 1999 FDA draft guidance for reducing the need for duplicate testing. Teva's Comment to FDA on Draft Guidance 3 (Nov. 15, 2000), *at* http://www.fda.gov/ohrms/dockets/dailys/00/nov00/112900/c00011.pdf (last visited Feb. 15, 2005).

APPENDIX I

2001 PHARMA REVIEW TIMELINE

The steps leading to the revision of Directive 2001/83/EC are summarized below.[294]

(1) In July 2001, the European Commission announced a comprehensive reform of the pharmaceutical legislation. Its proposed Directive amending Directive 2001/83/EC [hereinafter revised Directive 2001/83/EC] was submitted to the Council of the European Union [hereinafter Council] and the European Parliament on November 26, 2001.[295]

(2) On June 26, 2002, the Council discussed the Commission's proposal for a revised Directive 2001/83/EC.[296]

(3) On September 18, 2002, the Economic and Social Committee (ESC) published its opinion on the proposed revised Directive 2001/83/EC.[297]

(4) On October 29, 2002, the Parliament's Committee on the Environment, Public Health and Consumer Policy [hereinafter the Committee] issued a first report making several amendments to the proposal for a revised Directive 2001/83/EC.[298]

(5) On October 23, 2002, the European Parliament voted on its first reading of the revised Directive 2001/83/EC, proposing several amendments to the report of the Committee.[299]

(6) On April 3, 2003, the Commission accepted several of the amendments made by the European Parliament. The revised proposal was sent back to the Council and the Parliament on April 24, 2003.[300]

(7) On June 2, 2003, the Council reached a political agreement on the common position regarding the revision of Directive 2001/83/EC.[301]

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[294] *More generally, see* Europarl, The Legislative Observatory, Procedure File for the Revision of Directive 2001/83/EC, *at* http://wwwdb.europarl.eu.int/oeil/oeil_ViewDNL.ProcedureView?lang=2&procid=5772 (last visited Feb. 15, 2005); European Commission, PreLex, *at* http://europa.eu.int/prelex/detail_dossier_real.cfm?CL=en&DosId=169782 (last visited Feb. 15, 2005).

[295] *See* European Commission, Proposal for a Directive of the European Parliament and of the Council Amending Directive 2001/83/EC on the Community Code Relating to Medicinal Products for Human Use (2002/C 75 E/13), (COM (2001) 404 final), OJ C75 E, 26.3.2002, at 216, *at* http://europa.eu.int/eur-lex/pri/en/oj/dat/2002/ce075/ce07520020326en02160233.pdf (last visited Feb. 15, 2005). *See also* Press Release, European Commission, Commission Proposes Comprehensive Reform of EU Pharmaceutical Legislation 3 (July 18, 2001) (IP/01/1027), *at* http://pharmacos.eudra.org/F2/review/doc/pr_i01_1027_en.pdf (last visited Feb. 15, 2005); European Commission, MEMO/01/267, *supra* note 248. *See* European Commission 2001 Proposal, *supra* note 248.

[296] *See* Council, 2440th Meeting, Health 13 (10090/02) (Presse 182), *at* http://ue.eu.int/pressData/en/lsa/71383.pdf (last visited Feb. 15, 2005).

[297] *See* Economic and Social Committee's Opinion, 2003 O.J. (C 61), 14.3.2003, at 1, *at* http://europa.eu.int/eur-lex/pri/en/oj/dat/2003/c_061/c_06120030314en00010008.pdf (last visited Feb. 15, 2005).

[298] *See* Committee Report (A5-0340/2002), *at* http://www2.europarl.eu.int/omk/sipade2?PUBREF=-//EP//NONSGML+REPORT+A5-2002-0340+0+DOC+PDF+V0//EN&L=EN&LEVEL=2&NAV=S&LSTDOC=Y (last visited Feb. 15, 2005).

[299] *See* European Parliament, 2003 O.J. (C 300 E) 11.12. 2003, at 20, 166, 183, 352-89 *available at* http://europa.eu.int/eur-lex/en/archive/2003/ce30020031211en.html (last visited Feb. 15, 2005). *See also* Press Release, European Commission, Commission Gives Qualified Welcome to European Parliament's Vote on Pharmaceutical Legislation, (IP/02/PHARMA VOTE-EN) (Oct. 23, 2002), *at* http://www.haiweb.org/pubs/pressreleases/vote-enfinal_oct2002.pdf (last visited Feb. 15, 2005).

[300] *See* European Commission, Amended Proposal for a [Revised] Directive [2001/83/EC] (COM(2003) 163 final - 2001/0253 (COD) - 2001/0254 (COD)) (Apr. 3, 2003), *at* http://europa.eu.int/eur-lex/en/com/pdf/2003/com2003_0163en01.pdf (last visited Feb. 15, 2005).

[301] *See* Council, 2512th Meeting, Employment, Social Policy, Health and Consumer Affairs 15 (9688/1/03 REV 1) (Presse 152), *at* http://europa.eu.int/comm/health/ph_determinants/life_style/mental_020603_en.pdf (last visited Feb. 15, 2005).

(8) On September 29, 2003, the Council reached a common position on the revised Directive 2001/83/EC, taking into account several amendments made by the Parliament.[302]

(9) On October 7, 2003, the Commission assessed, and expressed its support of, the Council's common position.[303] On that same date, the European Commission transmitted its position to the Council and to the European Parliament.

(10) On December 2, 2003, the Committee issued its recommendations to the Parliament.[304]

(11) On December 17, 2003, the European Parliament adopted, during its second reading, a resolution on the revised Directive 2001/83/EC, making some changes to the common position proposed by the Council.[305]

(12) On February 17, 2004, the European Commission gave its favorable opinion as to the latest changes adopted by the European Parliament during its second reading.[306] The Commission transmitted its opinion to the Council and the European Parliament.

(13) On March 11, 2004, the Council approved the proposal for a revised Directive 2001/83/EC (second reading).[307] The amendments as finally voted were made available on February 25, 2004.[308]

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[302] *See* Council, Common position adopted by the Council with a view to the adoption of a Directive amending Directive 2001/83/EC, OJ 297 E p.41-71 (Dec. 29, 2003), *at* http://europa.eu.int/eur-lex/pri/en/oj/dat/2003/ce297/ce29720031209en00410071.pdf (last visited Feb. 15, 2005); Council, Common position adopted by the Council with a view to the adoption of a Directive amending Directive 2001/83/EC (10950/03) (2001/0253 (COD)), (Sept. 22, 2003), *at* http://pharmacos.eudra.org/F2/pharmacos/docs/Doc2003/oct/AISAAAE.pdf (last visited Feb. 15, 2005).

[303] *See* European Commission, Communication to the European Parliament Concerning the Common Positions Adopted by the Council Regarding the Revision of Directive 2001/83/EC (SEC/2003/1082 final - COD 2001/0252 - COD 2001/0253 - COD 2001/0254), *at* http://europa.eu.int/smartapi/cgi/sga_doc?smartapi!celexplus!prod!CELEXnumdoc&lg=en&numdoc=52003SC1082 (last visited Feb. 15, 2005).

[304] *See* Committee's Report (adopted Nov. 27, 2003) (A5-0446/2003), *at* http://www2.europarl.eu.int/omk/sipade2?PUBREF=-//EP//NONSGML+REPORT+A5-2003-0446+0+DOC+PDF+V0//EN&L=EN&LEVEL=1&NAV=S&LSTDOC=Y (last visited Feb. 15, 2005).

[305] *See* Press Release, Landmark Agreement on Reforms of EU Pharmaceutical Legislation, IP/03/1771 (Dec.18, 2003), *at* http://europa.eu.int/rapid/pressReleasesAction.do?reference=IP/03/1771&format=HTML&aged=0&language=en&guiLanguage=en (last visited Feb. 24, 2005). The debates are available from http://www2.europarl.eu.int/omk/sipade2?L=EN&PUBREF=-//EP//TEXT+CRE+20031216+ITEM-006+DOC+XML+V0//EN&LEVEL=3&NAV=X and http://www2.europarl.eu.int/omk/sipade2?L=EN&PUBREF=-//EP//TEXT+CRE+20031217+ITEMS+DOC+XML+V0//EN&LEVEL=3&NAV=X (last visited Feb. 24, 2005). *See also* European Parliament, Legislative Resolution on the Common Position Adopted by the Council With a View to Adopting a European Parliament and Council Directive Amending Directive 2001/83/EC on the Community Code Relating to Medicinal Products for Human Use (10950/03/2003 - C5-0464/2003 - 2001/0253(COD)), (Codecision Procedure: Second Reading) (P5_TA-PROV(2003)0577, A5-0446/2003), *at* http://www3.europarl.eu.int/omk/omnsapir.so/pv2?PRG=CALDOC&FILE=20031217&LANGUE=EN&TPV=PROV&LASTCHAP=14&SDOCTA=5&TXTLST=1&Type_Doc=FIRST&POS=1 (last visited Feb. 15, 2005).

[306] *See* Opinion of the Commission on the European Parliament's Amendments to the Council's Common Position Regarding the Proposal for [a Revised Directive 2001/83/EC] (COM(2004) 124 final) (Feb. 17, 2004), *at* http://europa.eu.int/eur-lex/en/com/pdf/2004/com2004_0124en01.pdf (last visited Feb. 15, 2005).

[307] *See* Press Release, Council (6649/04) (Mar. 11, 2004), *at* http://www.consilium.eu.int/pressData/en/misc/79378.pdf (last visited Feb. 15, 2005).

[308] *See* document (2001/0253 (COD), PE-CONS 3613/04), *at* http://register.consilium.eu.int/pdf/en/04/st03/st03613.en04.pdf (last visited Feb. 15, 2005).