

Data and Marketing Exclusivity for Pharmaceuticals in the European Community

RICHARD F. KINGHAM*

GRANT H. CASTLE**

I. INTRODUCTION

Most industrialized countries now recognize the importance of data protection and marketing exclusivity to innovation in the pharmaceutical sector.¹ Although patents remain the key form of intellectual property, they often are insufficient to provide the incentive needed to develop new uses for old chemical entities. In addition, patents for biotechnology products and other innovative pharmaceuticals often are the subject of complex disputes, so that companies cannot be certain that a patent will guarantee a period of market exclusivity after regulatory approval is granted.

This article considers the measures that have been taken by the European Community (EC) to provide periods of data or marketing exclusivity for pharmaceutical products. It summarizes the rules on abridged marketing authorization applications (the EC equivalent of abbreviated new drug applications (ANDAs)) and discusses the recent proposal for a regulation on medicinal products for rare diseases.

The article concludes that the existing rules on abridged applications are deficient in significant respects: after more than thirteen years, many important issues still are undecided, and the key question whether to provide data protection for new uses of old products has been decided the wrong way. The recent proposal for an “orphan drug” regulation² is drafted more effectively than the provisions on abridged applications, but important issues still are unresolved.

II. BACKGROUND

Council Directive 65/65/EEC,³ adopted in January 1965, required EC member states to establish systems for premarket approval of medicinal products and specified the information required for marketing authorization applications, including reports of pharmacological and toxicological tests and clinical studies. The directive also

* Mr. Kingham is the Managing Partner of the law firm of Covington & Burling, London, UK office.

** Mr. Castle is an Associate in the law firm of Covington & Burling, London, UK office.

¹ As used in this article, the term “data protection” means a period of protection against submission or approval of marketing authorization applications that do not contain full safety or efficacy data, but refer (without the innovator’s permission) to data contained in the marketing authorization application for an innovative product (e.g., the periods of protection against approval of abbreviated new drug applications under section 505(j) of the Federal Food, Drug, and Cosmetic Act of 1938, Pub. L. No. 75-717, 52 Stat. 1040 (1938) (codified as amended 21 U.S.C. § 355(j) (1994)). “Marketing exclusivity” means a period of protection against approval of marketing authorization applications for similar products, even if they are supported by full safety and efficacy data (e.g., the seven-year period of exclusivity afforded to orphan drugs under 21 U.S.C. § 360cc).

² Regulation (EC) No. 141/2000 of the European Parliament and of the Council on Orphan Medicinal Products, 2000 O.J. (L 18) 1 [hereinafter Orphan Drug Regulation].

³ Council Directive 65/65/EEC of January 26, 1965 on the approximation of provisions laid down by law, regulation, or administrative action relating to proprietary medicinal products, Council Directive 65/65, 1965 O.J. (No. 22) 368, *reprinted in* 1965-1966 O.J. Spec. Ed. 20 (1972). The Commission has proposed a recodification of the medicines directives, under which all directives issued since 1965 will be consolidated and their provisions renumbered. Proposal for a European Parliament and Council Directive on the Community Code Relating to Medicinal Products for Human Use, COM(1999)315 final.

provided for submission of applications containing published reports in lieu of original safety and efficacy data, but did not establish a procedure for applications that omitted such data entirely.

Council Directive 75/318/EEC,⁴ adopted in May 1975, established detailed requirements for scientific dossiers submitted in support of marketing authorization applications. Council Directive 75/319/EEC,⁵ adopted at the same time, established a "multi-state" approval procedure (an early form of mutual recognition, without provision for mandatory EC decisions) and created the Committee for Proprietary Medicinal Products (CPMP) to oversee the procedure.

Council Directive 87/21/EEC,⁶ adopted in December 1986, amended Directive 65/65 to provide for acceptance of abridged applications, subject to data protection periods and other limitations, and revised the provisions relating to literature-based applications. The basic data protection period was six years, but member states were given the option of establishing a ten-year period or recognizing no data protection after the patent expired. Biotechnology and other high-technology medicines approved under a "concertation" procedure established by Council Directive 87/22/EEC⁷ were entitled to a uniform ten-year period of data protection.

Council Directive 93/39/EEC,⁸ adopted in June 1993, established a mutual recognition procedure, backed up by binding EC decision-making power, to replace the old multi-state system. The procedure took effect on January 1, 1995, and became mandatory for marketing authorization applications for the same product submitted to more than one member state after January 1, 1998.

Council Regulation (EEC) No. 2309/93,⁹ adopted in July 1993, created a centralized approval system for biotechnology and high-technology medicinal products (replacing the old concertation procedure) and provided that products approved through that system would benefit from the ten-year protection period. The centralized procedure, which took effect on January 1, 1995, is administered by the European Agency for Evaluation of Medicinal Products (EMA). Marketing authorizations are granted by the European Commission (or the Council of the European Union), acting on the advice of the CPMP, which is now established in the EMA.¹⁰

On July 28, 1998, the European Commission proposed a regulation on orphan medicinal products that would afford ten years of marketing exclusivity for designated products.¹¹ The Orphan Drug Regulation was adopted in December 1999 and

⁴ Council Directive 75/318/EEC of 20 May 1975 on the approximation of the laws of Member States relating to analytical, pharmacotoxicological and clinical standards and protocols in respect of the testing of medicinal products. Council Directive 75/318, 1975 O.J. (L 147) 1.

⁵ Council Directive 75/319/EEC of 20 May 1975 on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products. Council Directive 75/319, 1975 O.J. (L 147) 13.

⁶ 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. Council Directive 87/21, 1987 O.J. (L 15) 36.

⁷ Council Directive 87/22/EEC of 22 December 1986 on the approximation of national measures relating to the placing on the market of high-technology medicinal products, particularly those derived from biotechnology. Council Directive 87/22, 1987 O.J. (L 15) 38.

⁸ Council Directive 93/39/EEC of 14 June 1993 amending Directives 65/65/EEC, 75/318/EEC and 75/319/EEC in respect of medicinal products. Council Directive 93/39, 1993 O.J. (L 214) 22.

⁹ 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. Council Regulation 2309/93, 1993 O.J. (L 214) 1.

¹⁰ For a discussion of the centralized and mutual recognition procedures, see Richard F. Kingham, Peter Bogaert & Pamela Eddy, *The New European Medicines Agency*, 49 FOOD DRUG COSM. L.J. 301 (1994).

¹¹ Proposal for a European Parliament and Council Regulation (EC) on Orphan Medicinal Products, 1998 O.J. (C 276) 7.

entered into force on January 22, 2000, when it was published in the *Official Journal of the European Communities*.¹²

III. SUMMARY OF RULES ON ABRIDGED APPLICATIONS

Article 4.8 of Directive 65/65 requires a marketing authorization application to contain results of “pharmacological and toxicological tests” and “clinical trials,” but article 4.8.a provides for exceptions when the applicant can demonstrate:

- i. That the medicinal product is “essentially similar to a product authorized in the country concerned by the application and that the person responsible for the marketing of the original . . . product has consented” to the use of the data in its file; or
- ii. “By detailed references to published scientific literature presented in accordance with Article 1 of Directive 75/318/EEC that the constituent or constituents of the medicinal product have a well established medicinal use, with recognized safety or efficacy and an acceptable level of safety”; or
- iii. That the medicinal product is “essentially similar to a product which has been authorized within the Community, in accordance with Community provisions in force, for not less than six years and is marketed in the Member State for which the application is made.” Member states have the option to apply a ten-year period to all medicinal products, or a six-year period that does not extend beyond the date of expiry of a patent protecting the original product. All member states must, however, recognize a uniform ten-year period for products approved through the concertation procedure under Directive 87/22 and the centralized procedure under Regulation 2309/93.

A proviso to article 4.8.a(iii) states that, when the medicinal product is intended for a different therapeutic use from that of the original product or is to be administered by different routes or in different doses, “the results of appropriate pharmacological and toxicological tests and/or of appropriate clinical trials must be provided, but it shall not be necessary to provide references relating to each individual constituent.” Finally, article 4.8.b states that “[i]n the case of new medicinal products containing known constituents not hitherto used in combination for therapeutic purposes, the results of pharmacological and toxicological tests and of clinical trials relating to the combination must be provided, but it shall not be necessary to provide references relating to each individual constituent.”

Marketing authorization applications submitted under articles 4.8.a(i) and (iii) are referred to as “abridged” applications. Although there is no official terminology, it is common to refer to applications under article 4.8.a(i) as “right-of-reference” or “informed consent” and those under article 4.8.a(iii) as “true abridged” applications. The provisions concerning new indications, dosage forms, and combinations of old ingredients in article 4.8.a and 4.8.b create the possibility for “hybrid” applications based partly on original tests or clinical trials.

Where there is consent, right-of-reference applications raise few significant legal issues. They will not be discussed further here, except to note that such applications can be submitted only after the application on which they are based has been approved. The following sections consider issues relating to bibliographic, true abridged, and hybrid applications.

¹² See Orphan Drug Regulation, *supra* note 2.

IV. BIBLIOGRAPHIC APPLICATIONS

Unlike articles 4.8a(i) and (iii), article 4.8.a(ii) is a stand-alone application, not an abridged application, and does not include provisions for data protection periods. Therefore, it could be interpreted as creating a loophole similar to that for "paper" new drug applications (NDAs) prior to enactment of the Drug Price Competition and Patent Term Restoration Act of 1984¹³ in the United States. In fact, it appears that some member states have used it for that purpose, and the European courts have not determined completely the limits of the bibliographic procedure yet.

Two provisions of article 4.8.a(ii) seem, however, to limit its scope: first, bibliographic applications are permitted only for constituents having "a well-established medicinal use, with recognized efficacy and an acceptable level of safety"; and second, such applications must contain the full particulars required by Council Directive 75/318 for original applications.

The first requirement may justify imposing more stringent requirements for acceptance of bibliographic applications for relatively new products and those whose medicinal uses are not well-known. There is some support for this interpretation in a 1995 judgment of the Irish High Court.¹⁴

A recent amendment to the annex to Directive 75/318, interpreting the requirements for well-established medicinal use under Directive 65/65,¹⁵ provides that a bibliographic application will not be accepted until "one decade" after the "first systematic and documented use of that substance as a medicinal product in the EU."¹⁶ Presumably, this ordinarily would require a marketing authorization, but it is conceivable that widespread use under named-patient regimes or open-label clinical trials might suffice.¹⁷

The second requirement, if strictly applied, could preclude bibliographic applications even for relatively old or well-known medicinal products. The full information required by Directive 75/318 is seldom available in the published literature. Published reports of clinical trials usually lack the patient-by-patient data needed to compile the tabulations contemplated by the directive, as well as information on the chemical characteristics of the batches of medicinal products used in clinical trials. Bibliographic applicants rarely have access to case report forms, which the directive requires applicants to make available to the authorities on request, and many clinical trials and nonclinical tests required by the directive (pharmacokinetic studies, special toxicology studies, etc.) are not published at all or appear only as abstracts.

The European Court of Justice (ECJ) addressed this issue in its judgment in the *Scotia* case,¹⁸ which was referred by an English court for a preliminary ruling. The

¹³ Pub. L. No. 98-417, 98 Stat. 1585 (codified at 15 U.S.C. §§ 68b-c, 70b (1994); 21 U.S.C. §§ 301 note, 355, 360cc (1994); 28 U.S.C. § 2201 (1994); 35 U.S.C. §§ 156, 271, 282 (1994)). See *Upjohn Mfg. Co. v. Schweiker*, 681 F.2d 480 (6th Cir. 1982); *Burroughs Wellcome Co. v. Schweiker*, 649 F.2d 221 (4th Cir. 1981).

¹⁴ *Scotia Pharmaceuticals Ltd. v. National Drugs Advisory Board*, unreported (on file with authors).

¹⁵ The proposed codification of Directive 65/65 changes the wording of 4.8a(ii).

¹⁶ Commission Directive 1999/83/EC of 8 September 1999 amending the Annex to Council Directive 75/318/EEC on the approximation of the laws of the Member States relating to analytical, pharmacotoxicological and clinical standards and protocols in respect of the testing of medicinal products. Commission Directive 1999/83, 1999 O.J. (L 243) 9; see also Directive 75/318/EEC, *supra* note 4. Directive 1999/83/EC amends Part 3 of the Annex to Directive 75/318/EEC by insertion of a new section I into that Annex.

¹⁷ There is no specific allowance for new uses of old substances or new pharmaceutical forms, although these might receive additional periods of data protection under Regulation 2309/93 or the recent European Court of Justice interpretation of article 4.8a(iii). See sections V (C), (D)(7), *infra*. Thus, bibliographic applications still might be used as an alternative to true abridged applications.

¹⁸ Case C-440/93, *Regina v. Licensing Authority ex parte Scotia Pharmaceuticals Ltd.*, 1995 E.C.R. I-2851.

UK authorities admitted that the marketing authorization application in question entirely omitted certain information required by Directive 75/318. The Court held that the national authorities could not grant a marketing authorization under article 4.8.a(ii) where the dossier did not contain “detailed references” to published scientific literature “presented in accordance with each of the requirements” of the directive.

In 1998, the Dutch courts dealt with similar issues involving a generic version of Bristol-Myers Squibb’s product TAXOL (paclitaxel). An appellate panel of the district court in Utrecht held that, in light of the ECJ decision in *Scotia*, the bibliographic application provision must be construed strictly and is intended to be used “by way of rare exception only.” In particular, the court held that bibliographic applications must contain detailed, patient-specific information, even though that is seldom included in published scientific literature.¹⁹

The European Commission’s Notice to Applicants (a guidance document concerning the rules for marketing authorization applications) takes a similarly narrow view of article 4.8.a(ii). It states that a bibliographic application must contain “all of the tabular formats” required for a “full” application, as well as information on the “impurity/related substances profile and the decomposition products arising during storage”; provides that, if the published literature is insufficient to meet the requirements of Directive 75/318, “the applicant must supplement missing data with appropriate additional studies”; and advises that summary documents, such as the European public assessment report (EPAR) prepared for products approved in the centralized procedure, will “generally not be considered to supply sufficient information to meet the requirements of Directive 75/318/EEC.”²⁰ A Communication issued by the Commission in July 1998 also stressed that bibliographic applications “are and have to stay, by definition, complete and independent (‘stand-alone applications’).”²¹

The recent amendment to the annex to Directive 75/318, however, may be read to weaken the *Scotia* ruling that bibliographic applications must contain the same information required for full applications. The preamble states that “bibliographic references” may include “other sources of evidence (postmarketing studies, epidemiological studies, studies conducted with similar products, etc.) and not just tests and trials . . . if an applicant explains and justifies the use of these sources of information satisfactorily.”²² The text of the amendment appears to permit information otherwise required by the Annex to Directive 75/318 to be omitted if “justification” can be given as to “why demonstration of efficacy can be supported although some studies are lacking.”²³

V. TRUE ABRIDGED APPLICATIONS

Article 4.8.a(iii) permits an applicant to omit reports of pharmacological and toxicological tests and clinical trials if the applicant demonstrates that its product is

¹⁹ Bristol-Myers Squibb B.V./het College ter Beoordeling van Geneesmiddelen, Rb., Utrecht, 22 April 1998, (ann. R.D.), unreported (transcript on file with authors). The district court’s decision was stayed pending an appeal to the Afdeling Rechtspraak van de Raad van State, the highest administrative court in The Netherlands, and the case was subsequently dismissed by agreement of the parties.

²⁰ EUROPEAN COMMISSION, THE RULES GOVERNING MEDICINAL PRODUCTS IN THE EUROPEAN UNION, NOTICE TO APPLICANTS-MEDICINAL PRODUCTS FOR HUMAN USE, PROCEDURES FOR MARKETING AUTHORIZATION, Vol 2A, at 6 (Office for Official Publications of the European Communities 1998) [hereinafter Notice to Applicants].

²¹ Commission Communication on the Community Marketing Authorization Procedures for Medicinal Products, 1998 O.J. (C 229) 4, 13 [hereinafter Commission Communication].

²² See *supra* note 16.

²³ It is possible that these provisions are intended mainly to simplify use of bibliographic applications for herbal products and phytomedicines, but there is nothing in the directive to prevent their use in reviewing applications for other medicinal products.

“essentially similar” to a product that: 1) has been authorized in the EC for the requisite number of years, and 2) is marketed currently in the member state where approval is sought. The following are key issues arising under this provision.

A. *Products to Which the Abridged Procedure Applies*

The rules in article 4.8 apply to all medicinal products that are within the scope of the marketing authorization requirement under EC medicines legislation. There is no separate approval procedure for biological products comparable to that created by the Public Health Service Act²⁴ in the United States. At one time, there were exemptions for certain immunological products, radiopharmaceuticals, blood derivatives, and homeopathic medicines, but these were eliminated largely by a series of “extension” directives adopted in 1989 and 1992.²⁵ Whole blood, plasma, and blood cells of human origin still are exempt, as are medicines (including plasma derivatives) that are not “industrially produced.”²⁶ In addition, some member states maintain special rules for products that were on the market when the EC marketing authorization requirements took effect, although the deadline for applying those requirements has now expired.

B. *Data Protection Periods*

Several data protection periods may apply under article 4.8.a(iii). The European Commission’s Notice to Applicants lists the following:

- Ten years in all member states for products approved under the centralized procedure.
- Ten years in all member states for products approved under the old concertation procedure established by Directive 87/22.
- Ten years for all other products in Belgium, France, Germany, Italy, The Netherlands, Sweden, and the United Kingdom.²⁷
- Six years for all other products in Austria, Denmark, Finland, Ireland, and Luxembourg.²⁸
- Six years for all other products in Greece, Spain, and Portugal, but this period will not be applied beyond the expiry of a patent protecting the original product.²⁹

²⁴ Public Health Service Act, Ch. 288, 37 Stat. 309 (codified at 42 U.S.C. §§ 201 et seq. (1994)), § 351, establishes a licensing requirement for vaccines and other biological products that is separate from the provisions for approval of new drugs in section 505 of 21 U.S.C. § 355.

²⁵ Council Directive 89/342/EEC of 3 May 1989, extending the scope of Directive 65/65/EEC and 75/319/EEC and laying down additional provisions for immunological medicinal products consisting of vaccines, toxins, or serums and allergens, Council Directive 89/342, art. 1, 1989 O.J. (L 142) 14; Council Directive 89/343/EEC of 3 May 1989, extending the scope of Directives 65/65/EEC and 75/319/EEC and laying down additional provisions for radiopharmaceuticals, Council Directive 89/343, art. 1, 1989 O.J. (L 142) 16; Council Directive 89/381/EEC of 14 June 1989, extending the scope of Directives 65/65/EEC and 75/318/EEC on the approximation of provisions laid down by law, regulation, or administrative action relating to proprietary medicinal products and laying down special provisions for medicinal products derived from human blood or human plasma, Council Directive 89/381, art. 1, 1989 O.J. (L 181) 44; Council Directive 92/73/EEC of 22 September 1992, widening the scope of Directives 65/65/EEC and 75/318/EEC in the approximation of provision laid down by law, regulation, or administrative practice relating to medicinal products and laying down additional provisions on homeopathic medicinal products, Council Directive 92/73, 1992 O.J. (L 297) 8.

²⁶ The status of processed cells and tissues of human origin remains unclear. There also are exceptions from the marketing authorization requirement for “magistral” and “officinal” formulas prepared by pharmacists and medicinal products supplied to named patients by physicians.

²⁷ Notice to Applicants, *supra* note 20, at 8.

²⁸ *Id.*

²⁹ *Id.* A review of national laws suggests that the Notice to Applicants may be over-simplified. In Spain and Portugal, the authorities may in some circumstances apply a data protection period beyond the expiry of a patent protecting the original product.

For products approved under the centralized procedure, the data protection period begins when the European Community issues a decision granting the marketing authorization. For products approved by national authorities, the period is measured from the first marketing authorization "within the Community, in accordance with Community provisions in force."³⁰ Thus, a lengthy delay between the first and subsequent approvals can have significant economic consequences, and it may be undesirable to seek approval in minor markets before regulatory issues are resolved in more important ones.

It generally is assumed that the provision relating to "Community provisions in force" was intended to preclude abridged applications based on licenses of right or "fictitious" approvals granted to products that were on the market when the EC authorization requirements were implemented, because there often would be no safety or efficacy data on file with respect to those products.³¹ Also, the provision should preclude abridged applications based on national approvals granted before countries entered the EC, because those products were not "authorized within the Community."³² But it may be possible to argue that approvals were granted "in accordance with Community provisions in force" if countries applied requirements consistent with EC medicines directives before entering the EC. Austria, Finland, and Sweden may have been obliged to do this under the European Economic Area (EEA) agreement, which applied to them before they entered the EC in 1995.³³ This issue is of current interest, because Central and Eastern European countries now seeking admission to the Community are committed under so-called Europe Agreements to take steps to harmonize their medicines laws with EC directives, and some have already done so.³⁴

C. Definition of "Essentially Similar"

Directive 65/65 contains no definition of the key term "essentially similar." According to the minutes of the Council meeting at which the 1986 amendment to the Directive was adopted, essential similarity was intended to encompass products having

. . . the same qualitative and quantitative composition in terms of active principles, and the pharmaceutical form is the same; and where necessary, appropriate bioavailability studies have been carried out"³⁵

The Commission's Notice to Applicants further states that "the concept of essential similarity also applies to different oral forms (e.g., tablets and capsules) with the same active substance for immediate release."³⁶

³⁰ See Council Directive 65/65/EEC, *supra* note 3, at art. 4.8a(iii).

³¹ In *Regina v. Licensing Auth. ex parte Monsanto PLC* [1997] 3 C.M.L.R. 402, (Q.B. 1996), the English High Court rejected the argument that, in deciding whether to accept an abridged marketing authorization application, the UK Medicines Control Agency was required to determine whether the data submitted in support of an approval granted in Germany more than ten years previously were sufficient to meet the requirements of Directive 75/318. The court held that it was enough for the agency to determine that Germany had implemented the EC medicines directives when the approval was granted.

³² See Council Directive 65/65/EEC, *supra* note 3, art. 4.8a(iii).

³³ The Swedish Medicinal Products Ordinance measures the period of data protection from the first approval in an EEA country. Medicinal Products Ordinance (SFS 1992:1752) (Official Translation, Ministry of Health and Social Affairs International Secretariat, 1992).

³⁴ It is conceivable that marketing authorizations for immunologicals, radiopharmaceuticals, and blood derivatives granted before the "extension" directives took effect were not "in accordance with Community provisions in force," and that data protection periods did not begin until the EC marketing authorization requirement was imposed.

³⁵ Notice to Applicants, *supra* note 20, at 7.

³⁶ *Id.*

The definition of essential similarity was considered by the ECJ in the *Generics* case, decided in December 1998.³⁷ The case, which was referred by an English court, concerned abridged marketing authorization applications submitted to the UK Medicines Control Agency (MCA) for copies of CAPOTEN (captopril), ZANTAC (ranitidine), and ZOVIRAX (acylcovir). Each of the innovative products was modified several times during the ten-year period following the first marketing authorization, with the addition of new indications, dosages, or dosage forms.

The ultimate question was whether any of these changes was entitled to a new data protection period. Unlike the U.S. Drug Price Competition and Patent Term Restoration Act,³⁸ article 4.8.a(iii) provides no guidance on this point. The 1986 Council minutes suggest that products are "essentially similar" if they are in different pharmaceutical forms or contain different quantities of the "active principles," but those terms are difficult to apply in practice, and there is no discussion concerning changes in labeling.

In these circumstances, the MCA attempted to fashion a policy based on a Commission regulation that governs "variations" to marketing authorization applications (the EC equivalent of supplemental NDAs).³⁹ That regulation identifies certain changes that are deemed so significant that they cannot be approved by means of a variation, but require a new marketing authorization application. The MCA reasoned that indications for which a new marketing authorization application was required should also be sufficient to warrant a new data protection period.⁴⁰

In an opinion offered to the ECJ in January 1998, the Advocate General (a court official) concluded that the variations regulation was irrelevant to the question of essential similarity, but he was troubled by the definition in the 1986 Council minutes, which would afford no additional period of data protection for new indications. He therefore suggested that an additional period of data protection might be appropriate for new indications that "constitute therapeutic innovations of great significance."⁴¹

In its judgment, however, the ECJ rejected this suggestion. It held that medicinal products will be deemed essentially similar if they have the same qualitative and quantitative composition in terms of active principles; have the same pharmaceutical form; and are bioequivalent.⁴² Products will not be deemed essentially similar, however, if it is apparent in light of scientific knowledge that they differ as regards safety or efficacy. If a generic product meets the criteria for essential similarity, it is entitled to all currently approved indications for the original product.

The judgment did not define the terms "active principle" or "pharmaceutical form." The Advocate General's opinion suggested that the definition of "pharmaceutical form"

³⁷ C-368/96, *The Queen v. The Licensing Auth. established by the Medicines Act 1968 (acting by The Medicines Control Agency), ex parte Generics (UK) Ltd., The Wellcome Found. Ltd. and Glaxo Operations UK Ltd. and Others*, 1998 E.C.R. I-7967.

³⁸ 21 U.S.C. § 355(j).

³⁹ 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, Commission Regulation 54/95, 1995 J.O. (L 55) 7.

⁴⁰ For example, a new application is required to add an indication in a "different therapeutic area," defined in terms of the third level of the WHO Anatomic Therapeutic Chemical Code.

⁴¹ Opinion of Mr. Advocate General Ruiz-Jarabo Colomer delivered on 22 January 1998. *The Queen v. The Licensing Auth. established by the Medicines Act 1968 (acting by The Medicines Control Agency), ex parte Generics (UK) Ltd., The Wellcome Found. Ltd. and Glaxo Operations UK Ltd. and Others*, 1998 E.C.R. I-7967, at para. 70. He suggested at para. 63 that an indication might be of such importance if it would have been eligible for centralized approval under Regulation 2309/93, was patentable under the Munich Convention or national patent law, or required testing similar in scope to that needed to secure approval of a new chemical entity.

⁴² See *supra* note 37.

contained in a publication of the Council of Europe is relevant.⁴³ It remains unclear whether the term “active principle” refers to the active ingredient or to the active moiety of a salt, ester, complex, or other derivative.⁴⁴

An essentially similar generic product is entitled to be approved in all dosage forms, doses, and dosage schedules currently approved for the original product. Different dosage forms that constitute new “pharmaceutical forms” presumably will receive additional periods of data protection, because they are not essentially similar under the definition adopted by the ECJ.

The ECJ did not explain what differences in “safety or efficacy” would defeat essential similarity. It may have had in mind the possibility that a generic product could contain an unsafe inactive ingredient or be formulated in a manner that made it less effective than the original product.

The ECJ required proof of bioequivalence as part of the essential similarity determination. A draft guidance document, prepared by the CPMP before the *Generics* case was decided, suggested that certain generic products might be approved without *in vivo* bioequivalence tests.⁴⁵ Special issues also may arise with respect to locally acting products (e.g., some topical and inhaled medicines) and certain biological and biotechnology products, for which clinical data may be required.

D. Other Issues

1. Relationship to Patent Laws

Unlike its U.S. counterpart,⁴⁶ article 4.8.a.(iii) is not linked directly to the patent status of the innovative product, except in those countries that have opted to limit the six-year data protection period to products with unexpired patents. In the United States, an ANDA may not be approved while a patent remains in effect unless there has been a judicial determination that a patent is invalid or will not be infringed. In the EC, once any period of data protection has expired, medicinal product agencies will approve abridged applications for products with valid, unexpired patents. The patent holder must then bring an action for infringement against the generic producer.

Occasionally, patent holders have secured injunctions against submission of

⁴³ Council of Europe, European Department for the Quality of Medicines, *Pharmeuropa List of Standard Terms*, (2d ed. 1998). The Council of Europe, an organization that is separate from the EC, prepared the publication at the request of the European Commission to assist in the application of provisions of Directive 75/318 that require use of “standard terminology” to describe the pharmaceutical form of a medicinal product in a marketing authorization application. The publication identifies twenty-one “standard terms” (e.g., oral preparations-solid forms), with specific dosage forms under each standard term (e.g., “capsules, hard”). In a recent case, the English High Court rejected the argument that another difference in formulation (use of a microemulsion versus a macroemulsion) constituted a different pharmaceutical form for the purposes of essential similarity. Judgment of Mr. Justice Hidden in *Regina v. Licensing Authority ex parte Novartis Pharmaceuticals UK Ltd.*, computer-aided transcript of the stenograph notes of Smith Bernal Reporting Ltd., Official Shorthand Writers to the Court (Q.B.D. Mar. 30, 2000).

⁴⁴ The Commission’s Notice to Applicants appears to adopt the view that different salts and esters are not essentially similar within the meaning of article 4.8.a.(iii), because it includes them among products that may require additional data under the “proviso” for hybrid applications. Notice to Applicants, *supra* note 20.

⁴⁵ CPMP, *Draft Note for Guidance on the Investigation of Bioavailability and Bioequivalence* CPMP/EWP/QWP/1401/98 (1998); see *Novartis*, *supra* note 43. In the *Novartis* case, the court suggested that medicinal product agencies have some discretion to determine whether proof of bioequivalence is required for essential similarity. The case is somewhat unusual because the dosage of the drug in question (cyclosporin) must be adjusted for each patient.

⁴⁶ 21 U.S.C. § 355(j).

samples to medicinal product agencies before patents expire, and the ECJ has held that a national court may use its injunctive powers to deny a generic company the advantage it gained by submitting samples before patent expiry.⁴⁷ But many member states do not routinely require samples, and those that do reportedly sometimes waive the requirement for generic applications.⁴⁸

The EC has not adopted a *Bolar* rule similar to that in the Drug Price Competition and Patent Term Restoration Act of 1984,⁴⁹ under which generic manufacturers may conduct tests necessary for marketing authorization applications without infringing patents.⁵⁰ Generic industry groups have made this a top legislative priority for many years, but innovative manufacturers strongly oppose it.⁵¹

2. Identifying the Reference Product

There is no official listing, comparable to the U.S. *Orange Book*,⁵² of products that are eligible for abridged applications. Innovators therefore cannot determine definitively what data protection periods will be recognized, and generic applicants sometimes have difficulty identifying a reference product. Medicines authorities in many member states will not release official information on the labeling of drug products approved in the past, and applicants may need to resort to unofficial documents, such as European versions of the *Physicians' Desk Reference*, to prove that innovative products were authorized in an EC member state six or ten years ago.

3. Accepting Generic Applications Before Exclusivity Periods Expire

Article 4.8.a(iii) operates as an exemption from the requirement to include pharmacological and toxicological tests and clinical trials in a marketing authorization application, and it should, therefore, compel medicinal product agencies to refuse applications submitted before data protection periods have expired. In fact, the Notice to Applicants specifies that “[e]vidence of the date of authorisation for more than 6/10 years and the confirmation that the medicinal product is marketed in the Member States concerned should be provided in the application for marketing authorisation.”⁵³ However, at least one national authority (the German Federal Institute for Drugs and

⁴⁷ Case 316/95, *Generics B.V. v. Smith Kline & French Lab. Ltd.*, 1997 E.C.R. I-3929. The Dutch court enjoined sales of the generic product for 14 months, the average time then required to review an abridged marketing authorization application in The Netherlands.

⁴⁸ According to the European Commission, samples are required routinely in Belgium, Italy, Luxembourg, The Netherlands, Portugal, Spain, and Sweden. They are submitted in other member states only when requested by the authorities. Notice to Applicants, *supra* note 20, at 154. The same is true in the centralized procedure.

⁴⁹ Pub. L. No. 98-417, 98 Stat. 1585 (codified in scattered sections of 15 U.S.C., 21 U.S.C., 28 U.S.C., and 35 U.S.C.).

⁵⁰ 35 U.S.C. §271(e)(1). The rule was enacted in response to the decision in *Bolar Pharmaceutical Co., Inc. v. Roche Products, Inc.*, 469 U.S. 856; 105 S. Ct. 183 (1984), which held that use of a patented medicinal product for bioequivalence tests required to support an ANDA was an act of infringement.

⁵¹ In a complaint to the World Trade Organization, the EC has taken the position that Canada's adoption of a *Bolar* rule, combined with an exception that permits generic manufacturers to “stockpile” medicinal products prior to patent expiry, is inconsistent with the Agreement on Trade-Related Aspects of Intellectual Property Rights, although no similar challenge appears to have been made against the original *Bolar* rule in the United States. Canada—Patent Protection of Pharmaceutical Products, complaint by the European Communities WT/DS114/1 (last modified Mar. 23, 2000) <www.wto.org/wto/dispute/bulletin.htm>.

⁵² FDA, APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS (18th ed. 1998).

⁵³ Notice to Applicants, *supra* note 20, at 8. A recently issued WTO Dispute Panel Report has upheld the provision of Canadian law permitting research and development activities for generic versions of medicines to begin before the patent term has expired for the innovative product, but ruled against the other provision that permitted pre-expiry stockpiling of generic products.

Medical Devices) reportedly accepts incomplete applications during the data protection period, reviews the sections relating to product quality, and issues the final approval shortly after the data protection period expires.

4. *Effect of Product Withdrawals*

Unlike U.S. law,⁵⁴ the EC medicines directives do not deal with the effect on generics when innovative products are withdrawn from the market. An abridged application is permitted under article 4.8.a.(iii) only if the product is essentially similar to one that "is marketed" in the member state where approval is sought. If the innovative product has been withdrawn from the market, it would seem impossible to meet this requirement. But there is no clear guidance from the Commission or the courts.⁵⁵

Article 4.8.a.(iii) also requires a generic applicant to demonstrate that an essentially similar product "has been authorized" within the Community for the requisite number of years, and does not clearly address cases in which the authorization for a reference product in another country is revoked before the six- or ten-year period expires. In practice, medicinal product agencies appear to accept generic applications in these circumstances, provided an essentially similar product is marketed within their territory when the abridged application is filed.

5. *Effect of Mutual Recognition Procedure*

In 1995, the EC instituted a system of mandatory mutual recognition of marketing authorizations for medicinal products. Article 10 of Directive 75/319, as amended by Directive 93/39, provides that member states may withhold recognition under this procedure only if "there are grounds for supposing that the authorization of the medicinal product concerned may present a risk to public health," which is defined in a footnote to refer to "the quality, safety and efficacy of the medicinal product."⁵⁶ This suggests that differing national data protection periods might not be a lawful reason for refusing to recognize an approval granted by another member state; a generic applicant might, for example, secure an approval in Greece immediately after a patent expires and demand recognition in other member states, although the six- or ten-year data protection period has not expired in those countries.

The European Commission has sought to deal with this issue in two guidance documents. The Notice to Applicants states that a company submitting an application for the mutual recognition procedure must "ensure . . . that there is a medicinal product authorized in the EU more than six or ten years previously . . ."⁵⁷ The Communication issued by the Commission in July 1998 states that:

[T]he product to which essential similarity is claimed must have been authorised within the Community, in accordance with Community provisions in force for not less than six (or ten) years. If the protection period is equal in all the concerned Member States, no problem will arise; if, however,

⁵⁴ 21 U.S.C. § 355(j)(5)-(6).

⁵⁵ This issue was raised in *Regina v. Medicines Control Agency ex parte Rhône-Poulenc Rorer Ltd.*, 46 B.M.L.R. 199 (Q.B. 1998). The innovator had withdrawn its old formulation from the market when a new, patented formulation was approved, but the Medicines Control Agency determined that both formulations were the "same product," and the court concluded that the question whether the reference product was "on the market" need not be decided.

⁵⁶ Notice to Applicants, *supra* note 20, at 15.

⁵⁷ *Id.* at 23.

the protection period in the concerned Member State is longer than in the reference Member State, mutual recognition in the concerned Member State is not possible before the expiry of the ten-year period.⁵⁸

Commission staff have informally suggested that they may consider amendments to article 4.8.a.(iii) to establish a uniform ten-year data protection period, but this undoubtedly would be controversial. If the issue cannot be handled through legislation, it most likely will be resolved in the courts.

Reportedly, some generic manufacturers also have attempted to use the mutual recognition procedure to avoid patent-infringement issues in member states that require applicants to submit samples. They argue that concerned member states (i.e., those in which recognition is sought) must accept a submission identical to that reviewed by the reference member state, and if that country did not require samples, the concerned member state cannot. The European Commission's Notice to Applicants does not support this contention, because it contemplates that concerned member states will follow the usual rules on samples in the mutual recognition procedure.⁵⁹

6. *Generic Versions of Pre-1995 Biotechnology Products*

A number of biotechnology products were approved by the member states before the centralized procedure took effect in 1995, and the safety and efficacy data relating to them are in the files of national agencies. Regulation 2309/93 requires, however, that all new marketing authorization applications for biotechnology products be submitted to the EMEA for review under the centralized procedure. Neither the regulation nor the Commission guidance documents clearly state where abridged applications for such products should be submitted: to the member states, which have the files but lack the legal competence, or to the EMEA, which has the legal competence but lacks the files.

In 1997, when the Commission circulated a preliminary draft of the Communication on marketing authorization procedures, its staff suggested that generic versions of pre-1995 biotechnology products should be reviewed by the member states. The final Communication states that the text of article 4 "implies that the abridged application can only be lodged with the authority that evaluated and authorized the original product as this authority holds the dossier on the medicinal product . . .,"⁶⁰ and it advises that abridged applications for products approved in the centralized procedure must be submitted to the EMEA. But it does not state expressly that abridged applications for biotechnology products approved by the member states can be submitted to national agencies. The question must be resolved reasonably soon, because patents and data protection periods will begin expiring soon for pre-1995 biotechnology products.⁶¹

7. *Data Protection for Centrally-Approved Products*

Article 13.4 of Regulation 2309/93 states that "[m]edicinal products which have been authorized by the Community in accordance with the provisions of this Regulation shall benefit from the ten-year period of protection referred to in point 8 of the

⁵⁸ Commission Communication, *supra* note 21, at 6.

⁵⁹ Notice to Applicants, *supra* note 20, at 24, 153-55.

⁶⁰ Commission Communication, *supra* note 21, at 6.

⁶¹ Article 3.5 of Regulation 2309/93 authorizes the Commission, acting with the member states in the Standing Committee on Medicinal Products for Human Use, to amend the lists of medicinal products for which centralized approval is required or permitted, and it is conceivable that the Commission may use this power to clarify the status of abridged applications for pre-1995 biotechnology products.

second paragraph of Article 4 of Directive 65/65/EEC.”⁶² This generally is interpreted to afford a ten-year data protection period to all products approved in the centralized procedure. While that interpretation certainly is correct for new chemical entities approved for the first time under Regulation 2309/93, it is less clear whether a ten-year exclusivity period will be afforded to products containing active ingredients previously approved through national procedures (e.g., products accepted under part B of the annex to the regulation, which permits centralized review of innovative indications, dosage forms, delivery systems, manufacturing processes, etc.). The courts well conclude that the question whether such products receive an additional exclusivity period depends on the principles established by the ECJ in the *Generics* case.

VI. HYBRID APPLICATIONS

Hybrid procedures, which permit applicants to rely on original data in addition to the exemptions available under abridged procedures, afford medicinal product agencies discretion to accept applications that might otherwise be rejected under article 4. Thus, article 4.8.a(iii) of Directive 65/65 permits approval of new uses, routes of administration, or doses of products that otherwise would be eligible for abridged applications, if “appropriate” data are provided; and article 4.8.b states that applications for new combinations of “known constituents” need not contain full data on the constituents, but only on the combination. The Commission’s Notice to Applicants summarizes the additional data that usually will be required for such hybrid applications, but leaves medicinal product agencies substantial discretion to determine the data required in particular cases.⁶³

The Notice to Applicants also states that bibliographic applications submitted under article 4.8.a(ii) may be supplemented with original clinical data if the published scientific literature does not contain all the required information.⁶⁴ Although the ECJ held in the *Scotia* case that member states lack discretion to approve bibliographic applications that omit information required by Directive 75/318, it is often difficult for competitors to determine what data actually were submitted. The member states ordinarily do not issue summaries comparable to the EPAR, which is released for centrally-approved products. Unless an innovative manufacturer obtains discovery through judicial procedures, it is often difficult to prove that a hybrid application lacks the data required by Directive 75/318.

VII. ORPHAN MEDICINES

In late 1999, following extensive study and consultation, the European Commission adopted the Orphan Drug Regulation.⁶⁵ The Regulation has direct effect, without the need for implementing legislation by the member states, and governs products submitted for approval under the centralized, mutual recognition, and national procedures.

Orphan product designations are issued by the Commission, acting on the advice of an expert committee, with representatives of the member states, patient organizations, and other interests. A designation will be granted if the product meets either of two tests: one based on prevalence criteria (the disease or condition must affect no more than five per ten thousand persons in the EC); and the other based on a determi-

⁶² See *supra* note 9.

⁶³ Notice to Applicants, *supra* note 20, at 10.

⁶⁴ *Id.* at 6.

⁶⁵ See Orphan Drug Regulation, *supra* note 2.

nation that it would be infeasible economically to develop the product without orphan drug incentives.⁶⁶

At first glance, these criteria seem similar in concept to those applied in the United States,⁶⁷ but the language of the Orphan Drug Regulation contains additional requirements. An orphan drug designation based on either the prevalence or economic feasibility criterion can be made only when "there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the Community or, if such method exists, that it can reasonably be expected that the medicinal product will be of significant benefit to those affected by that condition."⁶⁸

Orphan medicinal products are entitled to ten years of marketing exclusivity, measured from the first approval in the EC. At the end of the fifth year, however, any member state can initiate proceedings to restrict that period to six years if it believes that the criteria for orphan designation no longer apply (e.g., because the prevalence of the disease has increased or the manufacturer is earning an "unreasonable" profit).⁶⁹ In addition, competitive products can be approved during the marketing exclusivity period if they are not "similar" to the original product or are safer, more effective, or otherwise clinically superior to it.⁷⁰

The Commission has recently issued a draft implementing regulation to clarify the criteria for the grant of orphan status and the documentary requirements for an application and to define "similar medicinal product" and "clinical superiority."⁷¹ A "similar medicinal product" is one that contains a similar active substance or substances as a previously authorized orphan drug, and which has the same intended therapeutic indication. The draft regulation contains a detailed definition of a "similar active substance."⁷² An orphan medicinal product may be found "clinically superior" if it provides a significant therapeutic advantage "over and above" any existing authorized orphan product on the basis of a more favorable risk-benefit ratio in a substantial portion of the patient population or if it otherwise makes a major contribution to diagnosis or patient care.⁷³

VIII. CONCLUSION

The debate on the proposed orphan medicines regulation has focused the attention of policymakers within the Commission and the European Parliament on the key role of marketing exclusivity in promoting the investments required to develop new pharmaceuticals. It is hoped that this experience will help the same policymakers

⁶⁶ *Id.* art. 1.

⁶⁷ 21 U.S.C. § 360bb(a).

⁶⁸ See Orphan Drug Regulation, *supra* note 2, art. 3.2(b).

⁶⁹ *Id.* art. 8.2.

⁷⁰ *Id.* art. 8.3.

⁷¹ Draft Commission Regulation laying down the provisions for implementation of the criteria for designation of a medicinal product as an orphan medicinal product and definitions of the concepts "similar medicinal product" and "clinical superiority." The Standing Committee on Medicinal Products for Human Use issued a positive opinion on the proposed Regulation on March 23, 2000, and final action is expected shortly.

⁷² *Id.* art. 3.3. A "similar active substance" is defined as an identical active substance or one that has the same principal features of molecular structure including (1) "isomers, mixtures of isomers, complexes, esters, salts, and covalent derivatives of the original active substance" or an active substance that has only minor differences in molecular structure from the original, e.g., a structure analogue; or (2) the same macromolecule or one that differs from the original only with respect to certain specified changes in the molecular structure; or (3) the same "radiopharmaceutical active substance or one that varies from the original only in radionuclide ligand, site of labelling or molecule-radionuclide coupling mechanism linking the molecule and radionuclide provided that it acts via the same mechanism."

⁷³ *Id.* art. 3.3.

understand the need for reform of the data protection provisions for other medicinal products. If those provisions are to serve their intended purpose, several major reforms should be considered.

First, the EC must make some provision to protect new uses for old chemical entities. Data protection is seldom a major issue in deciding whether to develop new chemical entities, for which adequate patent protection is assured almost always. The difficult judgments instead concern new indications for old compounds, for which patent protection often is ineffective or entirely unavailable. There are numerous examples of old compounds for which major new indications have been discovered, often with important implications for public health (e.g., aspirin for prevention of stroke, myocardial infarction, and more recently, spironolactone for treatment of congestive heart failure). 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.

Second, the EC should require member states to adopt a uniform ten-year data protection period for all medicinal products.⁷⁴ The existing scheme, with its varying local rules, creates confusion and uncertainty. Moreover, the provision of article 4.8.a.(iii) allowing member states to offer no data protection period beyond the expiry of a patent undermines the Community's position in international negotiations and, at least as applied to new chemical entities, arguably is inconsistent with the obligations of EC member states under the Agreement on Trade-Related Aspects of Intellectual Property Rights.). Article 39(3) provides that members "when requiring, as condition of approving the marketing of pharmaceutical . . . products which utilize new chemical entities, the submission of undisclosed test or other data, the origination of which involves considerable effort, shall protect such data against unfair commercial use. . . ."⁷⁵

Third, the EC should establish a register or other formal document, similar to the *Orange Book* in the United States, by which interested persons can determine the data protection periods of approved products. It may be impracticable to establish such a list for products previously approved by the member states, but it should be possible to establish one prospectively. A list is not only desirable to inform competitors when they may submit generic applications, but to confirm innovators' expectations.

Finally, article 4.8.a(ii) should be amended to provide the same periods of data protection for bibliographic applications as for true abridged applications, including periods of protection for new indications and other changes that are entitled to data protection under the amended version of article 4.8.a(iii). This will not undermine the use of bibliographic procedures for herbal medicines and similar products (which appears to be the main concern of the Commission and several member states), but will prevent the use of those procedures to subvert the data protection provisions of article 4.8.a.(iii).

⁷⁴ This was, in fact, the original proposal advanced by the Commission, but was rejected later for political reasons. See Report from the Commission to the Council Concerning the Adoption of Certain Urgent Measures Intended to Facilitate the Development and Marketing of Medicinal Products Derived From Biotechnology and Other High Technology Medicinal Products in the Community, COM(84)437 final.

⁷⁵ Agreement on Trade-Related Aspects of Intellectual Property Rights, Apr. 15, 1994, Marrakesh Agreement Establishing the World Trade Organization, Annex 1C, LEGAL INSTRUMENTS—RESULT OF THE URUGUAY ROUND, vol. 31; 33 I.L.M. 81 (1994).

