

THE EUROPEAN UNION'S PHARMACEUTICAL AUTHORIZATION PROCESS

**Linda R. Horton, Partner
Hogan & Hartson LLP
Washington, DC and Brussels Belgium
LRHorton@HHLaw.com**

September 2007

© Hogan & Hartson LLP; all rights reserved, with permission granted to Law Seminars International to distribute and use document for the September 28, 2007 Biotechnology Conference, Seattle, Washington.

THE EUROPEAN UNION'S PHARMACEUTICAL AUTHORIZATION PROCESS

Introduction

This report on European Union (EU) regulation answers seven questions:

- who regulates pharmaceuticals (page 2)?
- what are the basic requirements (page 4)?
- what authorization options are available (page 6)?
- what about generics (page 12)?
- what about biosimilars (page 18)?
- how does a product developer get scientific advice (page 21)? and
- how does the EU regulate good manufacturing practices (GMPs) (page 26)?

Development of pharmaceuticals is a challenging process, and the regulatory gateways to the marketplace are complex. Nowhere is this more true than in the EU, which is made up of 27 different countries. Fortunately for pharmaceutical developers, in the world's two largest pharmaceutical markets, the EU and the United States, regulators and industry have made significant progress toward harmonizing many regulatory requirements relating to product development, through the International Conference on Harmonization (ICH). This report focuses upon distinctive aspects of EU regulation, but bear in mind that ICH documents are always relevant in an EU context.

I. Who regulates pharmaceuticals?

EU regulation of “medicinal products”—as pharmaceuticals are called in the relevant EU legislation—is a rapidly changing work in progress. Without question, the European Medicines Agency (EMA) has emerged as the principal pharmaceutical regulatory body in Europe. In the short time since it began operations in 1995, this Agency has become an international heavyweight able to hold its own even with the U.S. Food and Drug Administration (FDA). Within the EU, the EMA is viewed as having so masterfully carried out the tasks originally entrusted to it, that its scope of responsibility has been steadily expanded.

According to the EMA website, the Agency's “mission statement is, in the context of a continuing globalisation, to protect and promote public and animal health by:

- developing efficient and transparent procedures to allow rapid access by users to safe and effective innovative medicines and to generic and non-prescription medicines through a single European marketing authorization,
- controlling the safety of medicines for humans and animals, in particular through a pharmacovigilance network,
- facilitating innovation and stimulating research, hence contributing to the competitiveness of EU-based pharmaceutical industry,
- mobilising and coordinating scientific resources from throughout the EU to provide high-quality evaluation of medicinal products, to advise on research and development

programmes, to perform inspections for ensuring fundamental GXP* provisions are consistently achieved, and to provide useful and clear information to users and healthcare professionals. (* GXP means 'good clinical practice' (GCP), 'good manufacturing practice' (GMP) and 'good laboratory practice' (GLP) collectively.)¹

The EMEA's key expert committee, the Committee on Medicinal Products for Human Use (CHMP), prepares opinions on whether individual products should be authorized for marketing in the EU. However, the actual authorization decision is made by the European Commission in Brussels. The Commission generally endorses the CHMP's opinion and must give reasons if it chooses not to do so.

The European Commission is the principal administrative body in the EU. It is headed by a President, currently the former Portuguese Prime Minister José Manuel Barroso. The Commission is comprised of Directorates-General corresponding to departments in the U.S. government. The department in the European Commission to which the EMEA forwards CHMP opinions is the Pharmaceuticals Unit of the Directorate-General on Enterprise and Industry (DG Enterprise). Other parts of the European Commission that are important in the public health area are the Directorate-General for Research and the Directorate-General for Health and Consumer Protection (DG SANCO), which oversees a new European Centre for Disease Prevention and Control (ECDC).

In the 12 years since the EMEA began operation, it has become the principal gateway to the European marketplace for new chemical entities, as well as the exclusive route to market for biotechnological medicines and a growing list of other products. Located in London, the EMEA is headed by an Executive Director, currently Thomas Lönngren, appointed by the agency's management board for a five-year term. The EMEA management board is principally responsible for budgetary matters. It consists of two Members of the European Parliament, two senior officials of the European Commission, one representative from each Member State (generally the head of its drug regulatory agency), and one representative each from patients' organizations, doctors' organizations, and veterinarians' organizations. Representatives of certain EU accession candidates and the three other European countries that are members of both the European Economic Area (EEA) and the European Free Trade Association (EFTA)--(Iceland, Liechtenstein and Norway)--participate as observers in board proceedings and certain other EMEA activities.

The EMEA has a budget of 154,538,000€ for 2007 and a staff of 500 highly trained professionals from all over the EU. The EMEA is able to operate with such a relatively small staff, compared to the thousands in FDA engaged in pharmaceutical regulation, because it functions in part as a secretariat. Most product reviews and guideline-drafting activities are carried out by Member State experts serving on the CHMP and other scientific groups. In fact, a large share of the EMEA's budget pays Member State drug regulatory agencies (called "competent authorities") for the scientific services of their experts in carrying out functions for the EMEA. In 2006, 36% of the EMEA's budget went to Member State regulatory agencies for these services.

The EU regulatory system's key distinguishing feature is that it essentially functions as a network: "The EMEA operates in partnership with the national competent authorities for human

and veterinary products in the Member States.... The authorities make scientific resources available in the form of a network of more than 3,500 European experts who assist the Agency in performing its scientific tasks.”² The national authorities include the United Kingdom’s Medicines and Health products Regulatory Agency (MHRA), the French Health Products Safety Agency (afssaps), the German Federal Institute for Drugs and Devices (BfArM) and Paul Ehrlich Institute (PEI), the Swedish Medical Products Agency (MPA), and others. Member State agencies have authority to approve certain products and they also carry out a host of important regulatory responsibilities including approval of clinical trials, inspections, and post-approval surveillance.

The principal contact point in Europe concerning the tests needed to satisfy EU requirements for authorization of a pharmaceutical is the EMEA. However, many if not most carefully designed product development plans also involve contacts with Member State experts. It must be borne in mind that, in Europe, there is no single, all-powerful focal point throughout the product development process that is analogous to the relevant review division in FDA’s Center for Drug Evaluation and Research.

II. What are the basic requirements?

Whether a product enters the EU market through the centralized or decentralized routes discussed below, there is a complex array of requirements and guidelines at both the EU and Member State levels dealing with preclinical testing and Good Laboratory Practices (GLPs), Good Clinical Practices (GCPs), Good Manufacturing Practices (GMPs) and related chemistry and manufacturing controls, inspections, labelling, advertising and promotion, parallel trade, imports, exports and compliance and enforcement. There has been a rapid expansion of law on these subjects at the EU level, with increased harmonisation in many areas. Still, Member State requirements and guidelines remain essential parts of the EU regulatory picture, and there are considerable differences in implementation and enforcement.

EU regulation is similar in many respects to regulation in the United States. Its detailed requirements in many areas are similar to FDA requirements, so the discussion which follows focuses on novel EU aspects.

No medicinal product can be placed on the market in the EU unless it has been authorized. This is in contrast to the U.S. system, in which a few categories of older drugs (most Over-The-Counter drugs handled by monographs and a shrinking number of prescription drugs) have been allowed to be marketed as “not new” drugs or pre-1938 “grandfathered” drugs. Three key laws govern the EU authorization procedure: the Clinical Trials Directive,³ the Community Code on Medicinal Products Directive,⁴ and the EMEA Regulation.⁵ Any time the EU lawmaking institutions⁶ decide to legislate via a “directive,” the 25 EU Member States must then implement that directive into their national law by means of statutes, regulations and other legally binding steps. Any EU “regulation,” such as the EMEA Regulation, takes effect throughout the EU upon the effective date stated in it, without need for any Member State action.

A. Clinical trials regulation is one of the areas in which the EU regulatory landscape has most changed in the last years few and is still undergoing modifications. This is largely as a result of

the Clinical Trials Directive and the Member State laws implementing its provisions into their national laws. The European Commission and the EMEA have issued many guidelines on clinical trials. However, all approval and supervision of clinical trials in the EU is carried out at the EU Member State level and the Clinical Trials Directive is a floor rather than a ceiling. Member States have layered many requirements on top of the EU-level basics, and legal research at EU Member State level is essential whenever there is one or more clinical trial sites in a country.

As a result, the Clinical Trials Directive has had only partial success in achieving harmonization of clinical trial regulation in the EU. We and others had predicted this problem back in 2005 when Member States were (belatedly) implementing the legislation. Now even the EU authorities are concerned. At least one expert who once worked for the MHRA and is now in industry has suggested that EU create an optional “EU clinical trial approval” via the EMEA. No company would be forced to take this pathway, but those that did could get a single approval to conduct the same trial in various EU countries with need only for local ethics committee approval. This proposal warrants consideration.

To explore how to improve the operation of the Clinical Trials Directive, the EMEA convened a workshop (London, October 2007) to discuss these issues. While the scheduling of this workshop will no doubt call attention to the burden of disparate regulation, anyone doing clinical trials in the EU, and especially in the UK, needs to keep in mind the trends in Europe going in the direction of more control, not less, over clinical trials.

In particular, the TeGenero incident in London in early 2006 focused the spotlight upon first-in-human clinical trials, generally conducted in healthy volunteers. *See Case Study : The TeGenero Incident on page 29.* The EMEA and several Member State agencies (MHRA and afssaps) have recently issued guidelines on first-time-in-humans clinical trials.

One question always raised is whether the EU authorities will accept data from clinical trials conducted outside the EU. The answer is “yes, but.” The EMEA and Member State authorities accept data from clinical trials conducted in non-EU countries. However, acceptance is conditional upon the application for marketing authorization containing a statement that clinical trials conducted outside the EU met the ethical requirements of the Clinical Trials Directive as well as Good Clinical Practice.⁷

Clinical trials conducted for EU authorities often include an active comparator arm. FDA and the EU authorities, with counterparts from Japan, worked together to develop the ICH E10 guideline on Choice of Control Group and Related Issues in Clinical Trials. The EU agrees with the FDA view that placebo groups are justified in many drug trials, and neither the FDA nor the EMEA has adopted the 2000 version of the *Declaration of Helsinki*⁸ which expresses a quite negative view of placebo-controlled trials. (FDA uses the 1989 version, and the EMEA the 1996 version, of the *Declaration*.) Drug companies report that, despite these areas of agreement, the EMEA is more likely than FDA to demand a clinical trial that compares the test drug against an active comparator. This expectation is believed to stem from the fact that, in many EU Member States, the government is a major purchaser of drugs and wishes to ensure availability of information concerning the relative efficacy and safety of products in the same therapeutic class.

III. What authorization options are available?

A. General requirements

Marketing authorization (approval) of medicinal products is regulated by the Community Code on Medicinal Products Directive and related Member State implementing legislation. Under these laws, the procedures for applying for marketing authorization, and the contents of applications, are essentially the same in all 27 EU Member States. The EMEA Regulation governs the authorization of medicinal products under the “centralized authorization procedure”. However, the provisions of the Community Code concerning the types of testing needed, and the contents of applications to be submitted, apply even to the EMEA procedure.

Under requirements which apply EU-wide and are spelled out in Annex I to the Community Code on Medicinal Products,⁹ an applicant must demonstrate the quality, safety and efficacy of any product for which authorization is sought in the EU. The Annex requires that the application follow the data content and format requirements in the ICH Common Technical Document (CTD),¹⁰ which seeks to harmonize the drug approval data requirements in Europe and other participating countries, including the United States. Any so-called Full Application must be accompanied by evidence that the necessary research and testing in animals and in human subjects has been conducted. The demonstration of quality, safety and efficacy of the drug is achieved through submission of information on the chemistry, manufacturing and pharmaceutical aspects of the product as well as the non-clinical and clinical data. (However, there also are various alternatives to Full Applications that are discussed below in the section on generics and biosimilars, on pages 13-15.)

Under the CTD, an application has five key parts, called Modules:

- Module 1, European Community Administrative Information (including, for example, a table of contents, Summary of Product Characteristics (SmPC),¹¹ environmental risk assessment, labeling and package insert samples, and information about experts who reported on the application);
- Module 2, Quality, Nonclinical and Clinical Summaries;
- Module 3, Chemical, Pharmaceutical and Biological Information for medicinal products containing chemical and/or biological active substances (considerable detail is required on ingredients and finished dosage form, relevance of European Pharmacopoeia, good manufacturing practices, products of animal origin, risks from adventitious agents, manufacturing process and composition of the active substances and finished drug products, inactive ingredients, etc.);
- Module 4, Nonclinical Reports (data from animal studies and laboratory tests on the drug’s safety and toxicity profiles, such as safe levels of exposure, how the drug works and affects certain organs and systems, how long the drug remains in the body, and whether a substance can cause cancer –all in animals); and
- Module 5, Clinical Study Reports (safety and efficacy data from studies of the drug’s therapeutic and other effects on human subjects, first in healthy subjects and then in the targeted patient population). Clinical studies must always be preceded by animal studies.

The application must include all information relevant to the product's evaluation, whether this information is favorable or unfavorable. It must include, in particular, all relevant details about any incomplete or abandoned preclinical or clinical tests, whether or not these related to a therapeutic indication for which marketing authorization is sought. The European Commission and the EMEA have developed additional guidelines that substantially clarify (and detail) the testing requirements and application procedure for authorization. Most important of these is the "Notice to Applicants," (NtA), a constantly updated, 10-volume publication covering all aspects of applications for marketing authorization in the EU. If printed off the European Commission website,¹² the NtA would occupy at least five linear feet of bookcase space. Several more shelves would be required for the EMEA's vast and growing collection of guidelines and similar documents which need to be consulted by pharmaceutical companies.

Most applications to the EMEA require an EU Risk Management Plan, according to a CHMP guideline adopted in 2005.¹³ Product samples are required only upon request.

Labeling is a key part of any application for marketing authorization. The Community Code on Medicinal Products, as well as the NtA and other Commission and EMEA guidelines, spell out in great detail what is required for labeling. In the EU, package leaflets for patients are required in all cases (aided by the fact that pharmaceutical companies generally must sell their products in multi-unit packs of typical dosage supply). Meanwhile in the United States, FDA-required patient insert labeling or MedGuides remain the exception rather than the rule.

Marketing authorizations granted by the European Commission or the Member States are valid for an initial five-year period. Following that period, market authorizations are unlimited, unless post-marketing safety evaluation (pharmacovigilance) leads the Commission or the relevant national authorities to impose an additional five-year renewal requirement.

B. Alternative Pathways

Under the EU system for authorizing medicinal products, there is both a "centralized authorization procedure" led by the EMEA, and an authorization procedure led by the Member State competent authorities in which the EMEA plays a much smaller role. New legislation became effective in late 2005 that both increased the proportion of products which must go through the centralized process and added to the existing mutual recognition process a new decentralized procedure.

1. The EMEA/Commission Centralized Authorization Procedure

In 2006, the EMEA received 79 initial applications for marketing authorization.

Where the centralized authorization procedure is used, an applicant submits one single marketing authorization application to the EMEA. A single evaluation is carried out through the CHMP, which is comprised of senior physicians and other experts from the Member State agencies. If the CHMP concludes that quality, safety and efficacy of the medicinal product is sufficiently proven, it adopts a positive opinion. The EMEA staff then send this to the Commission which, if

it agrees with the CHMP's positive opinion, adopts a decision granting a single market authorization valid for the whole of the EU.

For some products, use of the centralized process is *mandatory* while for others it is *optional*. The EMEA Regulation identifies the following types of products as ones for which centralized authorization is mandatory: medicinal products developed by means of recombinant DNA technology, controlled expression of gene coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells, hybridoma and monoclonal antibody methods, and orphan medicinal products. In addition, medicinal products for human use containing a new active substance which was not authorized in the EU on the date of entry into force of the revised EMEA Regulation (May 20, 2004) *and* are intended for treatment of specified diseases are subject to the *mandatory* centralized procedure. These diseases are acquired immunity deficiency syndrome, cancer, neurodegenerative disorder and diabetes. Starting May 20, 2008, products intended to treat auto-immune diseases and other immune dysfunction and viral diseases will also fall within the mandatory centrally authorization procedure.

One category of medicinal products where use of the centralized process is *optional*—at the option of the applicant—is where a product contains a new active substance that had not been authorized in the EU on the date of entry into force of the EMEA Regulation. This is a route the applicant can choose for cases where the new substance is non-biotech and its intended indication is something other than the diseases (AIDS, cancer etc.) whose treatments are subject to the mandatory centralized procedure, as discussed above.

Another category eligible for the *optional* use of the centralized procedure is where an applicant demonstrates that a product constitutes a significant therapeutic, scientific or technical innovation or can demonstrate that the granting of authorization in accordance with the EMEA Regulation is in the interest of patients at Community level. This category is potentially broad.

While the EMEA Regulation clearly requires that medicinal products intended for the *treatment* of diseases subject to the EMEA's mandatory jurisdiction (e.g., AIDS) must be approved under the centralized procedure, the legislation does not mention products for the *prevention* of such diseases. However, Guidelines on the therapeutic areas that fall within the mandatory scope of the centralized procedure recommend that applicants seek optional authorization under the centralized procedure for products aimed at preventing disease conditions for which treatment products are under the EMEA's mandatory jurisdiction.

An application submitted for authorization of a medicinal product in the centralized authorization system is submitted to the EMEA and reviewed by the CHMP. In its review, the CHMP takes into account appropriate benefit/risk scenarios in the populations and conditions of use as documented in the submitted clinical data. No medicine is considered free of risks or possible side effects, but the overall assessment must satisfy the reviewers and the CHMP as a whole that the benefits of using the new product outweigh the known or predicted risks.

After an application for authorization is submitted, an EMEA staff member is selected as Product Team Leader. However, the actual in-depth review of an application is carried out by a

“rapporteur” and a “co-rapporteur”, both appointed from among the members of the CHMP. A CHMP guideline governs appointment of these individuals¹⁴. The CHMP is made up of one expert per EU Member State plus a few extra members (so-called “co-opted members”) to round out the committee’s expertise. The rules of procedure of the CHMP permit it to establish and consult with expert groups known as “working parties” composed of members selected from a European experts list maintained by the EMEA. The CHMP currently has several working parties (11 in 2006) and a number of temporary working parties. The CHMP consults its working parties on scientific issues relating to their particular field of expertise, and delegates certain tasks to them associated with the scientific evaluation of marketing authorization applications or the drafting and revision of scientific guidance documents.

In addition, the CHMP has several scientific advisory groups. The role of the scientific advisory groups is to provide advice on the evaluation of specific types of medicinal products. They consist of European experts possessing expertise in various medical specialties.

When an application for authorization is ready for CHMP consideration at one of its 11 meetings per year, the matter is put on the agenda well in advance. Both the applicant and the rapporteur address the CHMP in writing and in oral sessions. CHMP members pose questions and seek additional information from both. There is almost always a list of questions for the applicant. Furthermore, a request for special commitments prior to authorization, such as addition of a warning or other information to labeling, may be made. Applicants also may be asked to submit a written commitment to conduct a post-authorization trial and submit its results to the CHMP, via the EMEA Product Team Leader. After these consultations and information exchanges, the CHMP provides its opinion to the EMEA and the European Commission. The opinion concerns whether, in light of the product’s safety, quality and efficacy and its overall benefit-risk ratio for its intended use, the product should be granted a marketing authorization in the EU. The opinion is announced in the press release issued by the EMEA at the end of each CHMP meeting. This generally is the first time the EMEA discloses to the public that an application for marketing authorization is pending.

To provide a picture of EMEA workload, in 2006, the EMEA received 79 initial applications for marketing authorization. In the same year, the CHMP adopted 51 positive opinions and four negative opinions as to products reviewed by it under the centralized procedure. An additional 8 applications were withdrawn from the review process by the applicants. (As with the FDA, applicants are permitted to withdraw their applications from the review process for any reason, and most applicants prefer this to a negative opinion.) Due to legislative changes effective in October 2005, the CHMP is required to publish a notice of each such withdrawal of an application from the review queue, along with the reasons for this action. The CHMP also publishes its reasons for any negative opinions on submitted applications.

The decision to grant or refuse an authorization is made by the European Commission. The Commission is not bound by the opinion of the CHMP. However, it must provide a justification if it chooses not to follow the opinion. In practice, the Commission generally follows the opinions of the CHMP. Each authorization decision is published on the Commission website in a register and also in the Official Journal (a publication similar to the U.S. Federal Register).

The CHMP assessment report of a medicinal product and the reasons for the favorable CHMP Scientific Opinion is made available on the EMEA website (<http://www.emea.europa.eu>), after consulting the applicant on deletion of any information of a commercially confidential nature. This document is called the European Public Assessment Report (EPAR) on a scientific opinion.

The CHMP can perform a benefit/risk review at any time. In some cases and taking into account the pharmacovigilance reporting received, CHMP can, revise its opinion based on the reassessment of the benefit/ risk profile of the product. Generally, this is in response to emerging information on safety issues with marketed products or referral by a Member State. Such revisions will be reflected in updates to the EPAR and in product information.

The EMEA and its CHMP have published a number of guidelines and similar documents. A noteworthy and relatively user friendly guide is the EMEA pre-submission guidance for Users of the Centralised Procedure – List of questions.¹⁵

Just as the CHMP publishes its reasons for any withdrawals of applications from the review queue as well as for any negative opinions on submitted applications, the CHMP also publishes its reasons when it decides that an authorized product should be taken off the market. The latter product-removal decision can pertain to *any* product marketed in the EU, whether it originally reached the market via the centralized route or one of the Member State authorization processes discussed below. Generally a reference to the CHMP of a product approved by Member States originates from a Member State agency in response to serious adverse events.

The EMEA and its CHMP have published a

2. Member State authorizations: the decentralized, mutual recognition, and national routes

A fundamental difference between the procedure for authorization of medicinal products in the United States and that used in the EU is the fact that there are, as mentioned above, two types of authority with the power to authorize medicinal products. These are

1. the European Commission (following EMEA review) and,
2. drug regulatory authorities of the EU Member States.

And there are three different types of marketing authorization that may be granted at national level in the EU Member States. These are: the new *decentralized procedure*, whereby one or more national marketing authorizations are granted in a coordinated manner; the *mutual recognition procedure*, whereby an authorization already granted by one EU Member State is recognized by the authorities of other Member States; and the *national authorization procedure*, a procedure that applies only to an authorization within a single EU country. As explained earlier, the format-and-content requirements and the standards of review of applications for marketing authorization are the same whether the applicant uses one of the national procedure routes and or is seeking authorization through the centralized EMEA/Commission procedure.

a. The decentralized procedure came into operation in late 2005. It is applicable in cases where a market authorization does not yet exist in any of the EU Member States for a specific medicinal product. Under the decentralized procedure, identical dossiers are submitted to all Member States

where a market authorization is sought. A Reference Member State, selected by the applicant, prepares draft assessment documents within 120 days of receipt of the application and sends these to the other EU Member States where authorization is sought (referred to as “Concerned Member States”). They, in turn, approve the assessment. If any of the Concerned Member States refuses to approve the assessment of the Reference State, various arbitration procedures are provided for by the Community Code.

The hope is that both the new decentralized procedure and the revised mutual recognition procedure, outlined below, will function better than the pre-2005 mutual recognition procedure. Restrictions have been placed on the ability of Concerned Member States to refuse to recognize the conclusions of the Reference Member State concerning an application for authorization. Such refusals must be based upon a Member State’s finding a potential serious risk to the public health; a European Commission guideline seeks to restrict such findings. Also, applicants are not allowed anymore to withdraw their applications from particular Member States that have raised concerns about the application. Rather, applicants must make use of new dispute resolution process involving a group comprised of senior Member State drug regulatory officials known as the Coordination Group for Mutual Recognition and Decentralized Procedures—Human (CMD(h)). If the CMD(h) cannot resolve the issue, an appeal to the EMEA is possible. Thus, *any* medicinal product, and regardless of when it was authorized or the procedure under which it was authorized, can come under CHMP scrutiny.

b. The mutual recognition procedure is used where an authorization has already been granted by a drug regulatory agency of an EU Member State. The principle of the mutual recognition procedure is that a Member State must recognize a decision made in another Member State authorizing a medicinal product unless the Concerned Member State considers that the product constitutes a potential serious risk to the to public health (note that this is the same standard as under the decentralized procedure discussed above). In such cases, the Reference Member State is notified of these concerns. The Member States involved are expected to find a solution within 90 days, which occurs in most cases. If the two Member States fail to find a solution within the prescribed time, the matter is submitted to the referral procedure discussed above in relation to the decentralized procedure.

Under the mutual recognition procedure, the assessment and marketing authorization granted by the Reference Member State should be mutually recognized by the other Concerned Member States. In the past this has not always occurred. However, it is believed that recent legislative amendments, paralleling those discussed above, have started to improve this procedure.

c. National authorizations have in the past been an important part of the European regulatory landscape but will have a more limited role in the future, particularly for sophisticated products. Today, an applicant interested in a drug product authorization in only one EU Member State may apply for such approval. The harmonized application and data requirements discussed above will still apply to the application, but the authorization granted allows a product to be marketed solely in that one State. In other words, this is not meant to be a regulatory shortcut. At one time, it was possible for an applicant to file a series of unlinked marketing authorization applications in various Member States. This option is no longer available. Current legislation restricts the national authorization option to the single Member State approval scenario. Where an applicant

is interested in marketing the product in more than one Member State, the application is subject to the new decentralized procedure described above, when an authorization of the product had not previously been granted, or to the mutual recognition process.

An option still available to a sponsor is to obtain a single national authorization and then seek mutual recognition of other Member States under the mutual recognition procedure discussed in the preceding section. This can even be done for a wholly new product (unless it is subject to the EMEA mandatory jurisdiction, as discussed earlier, but many companies interested in the Member State approvals might find the more structured decentralized procedure more suitable for their product.

Also, it bears repeating that, even when a product does not appear to qualify for EMEA's mandatory jurisdiction, and is not a new chemical entity, its sponsor can ask the EMEA to assess the product.

IV. What about generics?

Striking the balance between innovator rights and generic opportunities has been one of the most contentious issues in EU medicines law. Amendments to the Community Code enacted in 2004 and effective in late 2005:

- brought into EU law a definition of “generic medicinal product” that codified case law;
- included a related pro-generic change with a definition of “global marketing authorization” aimed at blocking innovators from seeking a restart of exclusivities through product changes;
- harmonized the EU regulatory data protection period, described as “8+2+1” (referring to the number of years in which an innovator's reference product is shielded from generic competition);
- created the opportunity for a generic company to submit an abridged application to a Member State regulatory agency other than the one that authorized the reference product; to use the centralized EMEA process for a generic copy of a centrally authorized product or to use (alternatively) a Member State process for a generic copy of a centralized product; and even to use the centralized EMEA process for generics of products originally approved by Member States;
- inaugurated a “Bolar” amendment to allow generic manufacturers to do testing during the reference product's patent life; and, last but not least,
- defined “similar biological medicinal product,” i.e., “biosimilar” as well as a pathway for their authorization, always through the EMEA/Commission centralized process.

A. Definitions

Under the Community Code,

‘generic medicinal product’ shall mean a medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies. The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance,

unless they differ significantly in properties with regard to safety and/or efficacy. In such cases, additional information providing proof of the safety and/or efficacy of the various salts, esters or derivatives of an authorized active substance must be supplied by the applicant. The various immediate-release oral pharmaceutical forms shall be considered to be one and the same pharmaceutical form. Bioavailability studies need not be required of the applicant if he can demonstrate that the generic medicinal product meets the relevant criteria as defined in the appropriate detailed guidelines.

A “reference medicinal product” is one authorized under the procedures applicable to Full Applications (such applications are discussed on the next page).

The new legislation introduces the term “global marketing authorization.” This term has absolutely nothing to do with the ICH Common Technical Document. Rather, it is a legal construct seeking to reduce innovators’ ability to claim that an innovation in its product warrants a new regulatory exclusivity period and is in many respects a companion to the new definition of “generic medical product” discussed above.

The relevant provision in the Community Code (Article 6.1) provides as follows:

When a medicinal product has been granted an initial marketing authorization in accordance with the first subparagraph, any additional strengths, pharmaceutical forms, administration routes, presentations, as well as any variations and extensions shall also be granted an authorization in accordance with the first subparagraph or be included in the initial marketing authorization. ...

It remains to be seen whether one global marketing authorization can restrict a later applicant, unconnected to the original marketing authorization holder, who wants a period of protection for a product improvement investment. There is a chance that slightly different wording in the EMEA Regulation, compared to the Community Code, might create a way for such second-comer innovations, from different companies, to have an exclusivity period of their own under the centralized procedure.

B. Types of Applications for Marketing Authorizations (“MAAs”)

To be approved in the EU, a generic drug must go through what is called an abridged product application process. There are several types of abridged applications. In most cases, generic companies must prove bioequivalence to the innovator’s reference product and, of course, meet such general requirements as GMPs and labelling and advertising controls. However, they do not need to conduct preclinical and clinical trials to prove product safety and efficacy, because the innovator’s submitted and approved dossier for the reference product is treated as having demonstrated safety and efficacy. The generic company does not have a right to obtain a copy of the reference product’s dossier but is allowed to refer the regulatory reviewer to that dossier, so long as the reference product is no longer under regulatory data exclusivity. As a practical matter, the regulator may not even need to refer to the reference product’s dossier, as the safety and efficacy of the active substance are treated as having been established by the innovator’s efforts.

It should be noted that, generally, an applicant has the option to “test its way to market,” even during the data exclusivity period, unless the reference product has orphan drug marketing exclusivity or the innovative company has brought a patent infringement case and obtained a judgment that bars the way. This testing option is not appealing to generic companies because their business model seeks to minimize the need for preclinical or clinical tests.

Several types of marketing authorization applications (MAAs) are available in the EU:

a. *Full (or Complete) Application.* As a frame of reference for what the generic applicant avoids by filing an abridged application, we refer here to a Full Application. It consists of the results of physicochemical, biological or microbiological tests; pharmacological and toxicological tests; and clinical trials. The data requirements are described in great detail in EU legislation and guidelines. A summary appears above, on pages 6 and 7.

b. *“Mixed Data” Applications.* These are applications in which published scientific literature is presented together with original test and trial results. Such applications must be submitted and processed following the complete, full and independent marketing authorization dossier requirements. This applies to the use of bibliographic references in mixed dossiers both as supportive data of a manufacturer’s own tests or trials or in order to replace any tests or trials in certain modules of the Annex to the Community Code Directive. All other modules are comparable to those found in a Full Application, as discussed above and on pages 6 and 7.

c. *Bibliographical Application.* It is possible to replace results of pharmacological and toxicological tests or clinical trials with detailed references to published scientific literature (information available in the public domain), if it can be demonstrated that the constituents of a medicinal product have a “well-established medicinal use,” with recognized efficacy and an acceptable level of safety. Bibliographical applications have been treated as a type of full and independent application. For example, there are old medicinal products that have long been marketed, but for which there is no original or reference product to which sameness or similarity could—in an abridged application—be claimed. Typically, these old medicinal products are well-established and have known indications, strengths and pharmaceutical forms. Due to the years in which they have been marketed and used, there generally is public information available about their safety and efficacy.

d. *Abridged Applications.* These are applications in which, subject to certain conditions, the applicant is not required to provide the results of pharmacological and toxicological tests or clinical trials, as they refer to information contained in the dossier of a reference product’s authorization. Among the possible types of abridged applications are:

(1). *Informed consent application*

The owner of certain privileged information gives or sells a right of reference to such data, which can be a right of reference to a full application, similar to the common use of master files covering substances contained in a medicine.

(2). Generic application

An application for a medicinal product claimed to be “essentially similar” to a reference medicinal product if the generic applicant demonstrates that its medicinal product is essentially similar to a reference product that has been authorized within the Community for the time period set forth in the relevant legislation on regulatory data exclusivity, discussed below.

The contents of an abridged application based on essential similarity are as follows:

- complete quality information (or documentation of consent to refer the regulator to the reference product’s file) together with data showing bioavailability and bioequivalence with the reference product, provided that the latter is not a biological medicinal product (particular requirements for biosimilars are specified separately);
- grounds for claiming essential similarity;
- summary and evaluation of impurities present in batches of the active substance(s) as well as those of the finished medicinal product;
- evaluation of bioequivalence studies or justification why studies were not performed in accordance with the European Commission Note for Guidance on the Investigation of Bioavailability and Bioequivalence;
- update of published literature relevant to the substance and the present application;
- discussion and substantiation (by published literature and/or additional studies) of every claim in the Summary of Product Characteristics not known or inferred from the properties of the medicinal product and/or its therapeutic group;and
- if applicable, additional data to demonstrate evidence of the equivalence of safety and efficacy properties of different salts, esters or derivatives of an authorized active substance.

(3). Hybrid abridged procedure

There are two possible hybrid abridged procedure scenarios:

- Where the active substance of an essentially similar medicinal product contains the same therapeutic moiety as the original authorized product [reference product] associated with a different salt/ester-complex/derivative evidence that there is no change in the pharmacokinetics of the moiety, pharmacodynamics and/or in toxicity which could change the safety/efficacy profile shall be demonstrated [with the admonition that, should this not be the case, this version shall be considered a new active substance].
- Where a medicinal product is intended for a different therapeutic use or to be administered by different routes or in different doses or with a different posology, the results of appropriate toxicological and pharmacological tests and/or of clinical trials shall be provided.

It is not required that the reference product to which a generic application refers be authorized at the time of the generic product application.

C. Regulatory data protection: “8+2+1” and “global marketing authorization”

Data exclusivity laws prevent regulators from reviewing or processing a generic manufacturer’s abridged marketing application that references the innovator’s clinical safety and effectiveness data, for a set period of time after the reference product’s marketing authorization is granted.

During this time period, a competitor may conduct its own original testing and clinical trials. However, a generic company that does not want to conduct trials of its own, but needs to prove that its product meets the legal standard, may be barred from referring the regulator to the innovator's data until the relevant data exclusivity period expires.

Patent protection (discussed briefly below on page 17) continues to be the primary mechanism to reward innovation and protect innovators' R&D investments from early generic competition that would erode incentives. An additional safeguard, known as regulatory data protection or exclusivity, is given to first-time innovators of new chemical entities and is also an important protection for undisclosed proprietary information. Providing such protection is required by Article 39.3 the World Trade Organization Agreement on Trade-Related Intellectual Property Rights (TRIPS).

Key elements of the 8+2+1 regulatory data exclusivity system are:

- 8 years' data exclusivity: during this period no generic applications may be filed (unless the follow-on application is based upon its own data or has the consent of the innovator);
- 2 years' marketing protection: generic applications may be submitted on the 8th anniversary of the reference product's marketing authorization's publication in the Official Journal but, postauthorization, they may not be marketed until the 10th anniversary of the innovator's authorization; and
- 1 additional year possible: for a new indication (or indications) that would offer significant clinical benefit and is authorized during the first eight years; if an innovator qualifies for the extra year, generic versions are barred from the market as to all indications until the 11th year has ended.

This harmonized exclusivity period applies throughout the EU for all approvals (centralized and decentralized) for which applications were submitted after October 30, 2005 or, in the case of applications to the centralized procedure, after November 20, 2005.

A generic company may submit its abridged application that references the innovator's data to EMEA or a Member State drug regulatory authority as early as the 8th anniversary of the innovator authorization. However, neither EMEA nor a Member State regulatory authority may approve and allow marketing of a generic product for two more years—or until the 10th anniversary of the reference product's authorization. Again, the "+1" would come into play if the innovator sought and obtained approval for a new indication during the first eight years of its product's exclusivity and was granted approval of the new indication. The result would be a total of 11 years of exclusivity. Also, there is a separate "+1" for a new use for a well-established product or for an Rx-to-OTC switch, as discussed below.

The semi-harmonized system preceding enactment of the new legislation will continue to be significant until at least 2012. The old "10/6" system continues to govern all applications submitted prior to 30 October 2005 or, in the case of applications to the centralized procedure, prior to November 20, 2005. Elements of the old 10/6 regulatory data exclusivity system were:

- centrally-approved products have a full 10 years, starting with authorization (publication by the European Commission of a decision granting the marketing authorization)
- nationally-approved products have either 10 or 6 years (Member States' choice):

- 10 years: Belgium, France, Germany, Italy, Luxembourg, Netherlands, Sweden, UK
- 6 years: Austria, Denmark, Finland, Greece, Ireland, Portugal, Spain and all the new Member States that joined the EU in 2004 (Cyprus, the Czech Republic, Estonia, Hungary, Latvia, Lithuania, Malta, Poland, Slovakia, and Slovenia).

There are two ways products already marketed can achieve regulatory exclusivity periods:

- a one-time, one-year data exclusivity period for a new indication for a well-established substance; and
- a one-year data exclusivity for change of classification (prescription to OTC).

European Commission guidelines provide details on what information must be submitted by companies seeking a one-year data exclusivity in these cases. Other product improvements do not earn the innovator the opportunity to request data exclusivity.

Orphan product marketing exclusivity was unchanged by the pharmaceutical review legislation. Since 2000, under the EU Orphan Drug Regulation, a company whose product had been designated as an orphan drug could, upon approval, receive 10 years of exclusivity. During that 10-year period, applications for the same therapeutic indication could not be accepted or approved. Marketing exclusivity is intended to allow the innovator to recoup its investment in a product that, because it is for rare diseases and conditions, would not otherwise attract the necessary interest among investors and manufacturers.

A Regulation providing a six-month extension for pediatric indications became effective in 2007.

D. Patent Law

EU patent law is beyond the scope of this document. However, in the interest of giving the reader a more complete picture of the balance of rights in Europe between innovators and generics, a brief summary of relevant provisions of patent law follows.

1. Patents

As elsewhere, European drug patents run for 20 years from the time of filing.

2. Supplementary Protection Certificates (SPCs)

Created by a 1992 Regulation, the SPC for part a medicine provides up to five years additional patent protection to compensate for part of the lost patent life between the time of patent filing and EU marketing authorization. SPCs help make up for the significant portion of that 20 years spent developing a drug product and obtaining regulatory approval.

In 1992, European authorities enacted a Regulation that created the SPC as a means of extending certain medicinal product patents, in order to compensate a patent holder for the elapsed time between filing the patent application and the product's first EU marketing authorization. An SPC may be granted once, at the expiry of patent protection.

In Europe, when an innovator company has a SPC for its product, a very long patent term is possible. These terms, extending as much as 25 years after patent filing, generally exceed the

applicable data exclusivity time periods. However, in some cases, the data exclusivity provisions discussed above can be a vitally important incentive for innovators by shielding products from generic competition long enough for some or all development investments to be recouped. Data exclusivity periods are particularly useful when: a product is, for one reason or another, not patentable; an innovator is unable to get a SPC; or product development and regulatory review take so long that the effective remaining patent life is short. Importantly, many biotechnology products could not be patented in the EU until a 1998 Directive was enacted on this subject; Member State implementation of this Directive still is spotty. Without a data exclusivity period, many innovative drugs might never reach the market.

The patent and data exclusivity systems complement one another to protect innovation. It is important to look not only at patent expiry (including any SPC) but also exclusivity period expiry. These time periods run entirely independently of one another.

For SPCs, there is a register at the European Patent Office of all SPCs filed and granted in any EU Member State. However, there appears to be no EU registry of products subject to unexpired data exclusivity periods, although such periods can be calculated from relevant authorization dates, where this information is available.

3. Bolar Provision

A harmonized EU-wide Bolar provision enables generic companies to start development work on a generic while the innovator's product is still under patent protection. The Community Code as amended provides that, "Conducting the necessary studies and trials with a view to the application of [provisions on abridged applications] and the consequential practical requirements shall not be regarded as contrary to patent rights or to supplementary protection certificates for medicinal products."¹⁶ Providing samples is considered a permissible activity.

This provision allows the use of patented drugs for generic testing and development work, in any EU country, without such "early working" being considered patent infringement. Prior to the enactment of the provision in 2004, testing a generic drug during the innovator product's patent life—to develop copies and test them for bioequivalence with the patented drug—was regarded by many EU countries (and the European Commission) as patent infringement. This EU Bolar provision is intended to keep both the technical expertise and the investment money involved in such work within the expanded EU and to allow generics to reach the market more quickly. Previously, companies conducted generic testing and trials outside the EU and used the results to submit an EU marketing authorization applications following the expiration of any patents and exclusivity periods.

V. What about biosimilars?

Before discussing the requirements for follow-on versions of biological products, we should make brief reference to specialized EU requirements for products derived from biotechnology.

A. General requirements relating to the release of genetically modified organisms affect the marketing authorizations of medicinal products that contain such organisms. When "GMOs" are incorporated into medicinal products, the relevant laws give regulators longer timeframes for

decisions on clinical trial applications. Fortunately, the intense opposition that has surrounded the marketing in Europe of genetically modified foods has not impeded the introduction of medicines with genetically modified components. European consumers can readily appreciate the value of recombinant biotech medicines, often safer and cleaner replacements of older biologicals derived from human donors, animals, or cadavers.

In general, biological medicinal products are regulated in precisely the same way as other medicinal products. Those derived from biotechnology must be reviewed by the EMEA, as discussed earlier. The European Commission has stated that only the EMEA has authority to assess applications for biotechnology-derived biosimilar applications. This flows from the EMEA's exclusive authority over biotechnology-derived medicines in general.

Also there are certain additional data requirements and testing requirements associated with biological medicinal products in general or particular types. Until legislative changes that became effective in late 2005, there was no such thing as an abridged application pathway for "biosimilar" versions of biological products. Even today, the general rule is a full application, with all the information required for full applications of chemical medicines, *and* in addition extensive additional information about the products and processes.

B. Biosimilars became a possibility in Europe due to the EU legislation enacted in 2004 and effective in October 2005 that amended the Community Code Directive to provide a definition of "similar biological medicinal product," popularly referred to as "biosimilars." Already the Annex to the Community Code on Medicinal Products that had been published in June 2003 had added provisions foreshadowing a streamlined pathway for biosimilars.

Article 10.4 of the amended *Community Code Directive* states, in its entirety:

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

The term "biogenerics" is also used, but is a misnomer because the copy cannot be identical to the reference product. In the United States, the terms "follow-on biologics" or "follow-on proteins" are commonly used.

The EU legislation provides a legal framework for biosimilars under which it is understood that these products will need less supporting data than had been required for the original reference product. A key question, answered in part by guidelines but also in discussions between follow-on applicants and regulators, concerns the data requirements for a biosimilar approval. As regulators are well aware, even experienced manufacturers have encountered serious immunogenicity problems as biologics production processes evolve.

c. Guidelines

The EMEA has issued a series of guidelines to detail biosimilar requirements:

- two comparability guidelines, December 2003;
- guideline describing general biosimilar approval principles, clinical and non-clinical issues;
- guideline describing general quality issues;
- annexes with more targeted guidance for product classes (human recombinant product classes containing erythropoietin, human growth hormone, granulocyte-colony stimulating factor and insulin).

The guideline on clinical and non-clinical requirements indicates that:

- Each application will be handled on a case-by-case basis.
- Each biosimilar applicant must justify its approach and is encouraged to seek early discussions with EMEA.
- The same reference product should be used for all application aspects (quality, safety and efficacy).
- A full quality dossier is required, as a biosimilar's safety/efficacy profile is highly dependent upon quality aspects.
- EMEA recommends the use, in required clinical trials, of the test product from the final manufacturing process.
- Certain clinical and nonclinical data are required:
 - Extensive nonclinical studies (in vitro and in vivo) and clinical trials of the biosimilar itself.
 - Immunogenicity data.

In addition, the biosimilar applicant must carry out an "extensive" comparability exercise to demonstrate that the product has a profile similar to the identified reference product, in terms of quality, safety and efficacy. Comparative pharmacokinetic studies to demonstrate equivalence are an essential part of this exercise.

In specifying clinical safety and pharmacovigilance requirements, the guideline distinguishes the pre-approval phase, which consists of safety data collected in preauthorization clinical studies, from the post-approval phase, which consists of close product monitoring. The biosimilar application should include a "risk specification" (describing possible safety issues arising from the fact that the manufacturing process differs from the innovator's) as well as a risk management plan, in accordance with EU legislation and guidelines. The guideline advises the applicant to have ready and in place, prior to approval, the pharmacovigilance systems and procedures (including traceability) needed to meet requirements. EMEA warns that compliance will be strictly monitored.

Each of the four annexes relates to one product class and provides proposed guidance on specific preclinical and clinical requirements for biosimilar applications, taking into account the special concerns of each class. For example, the erythropoietin annex states that efficacy trial safety data from at least 300 patients treated with a biosimilar are considered adequate for a premarket safety database (a number that many observers found shockingly small). Postmarket reporting will add to this database. The applicant also should provide at least 12 months of

immunogenicity data in patients treated with the biosimilar. Retaining samples for both titration and maintenance studies is recommended. A validated, highly sensitive assay should be used to detect anti-epoetin antibodies. EMEA has excused erythropoietin biosimilars from many safety studies that were carried out by the innovator companies.

The final guideline states that, “in case the reference product has more than one indication the efficacy and safety of the biosimilar must be justified or demonstrated separately for each of the claimed indications” and that the biosimilar applicant must consider the risk of immunogenicity separately for each indication. Nevertheless, the annexes on somatropin and on erythropoietin each has a section entitled, “extension of indication,” under which a demonstration of efficacy and safety in the most sensitive clinical model (renal failure, for erythropoietin) allows the biosimilar to be labelled with all the reference product’s other indications, given the same mode of action and justification by current scientific knowledge. Early biosimilar authorizations suggest that biosimilar applicants for other product classes will be allowed use of indications other than those covered in their clinical trials.

Another key issue is the extent to which regulators can rely upon innovators’ data in agency files to reduce generic data requirements; clearly EMEA should refrain from any reliance upon data in the reference medicinal product’s dossier. The generally accepted interpretation of the last sentence in the biosimilars definition—“The results of other tests and trials from the reference medicinal product’s dossier shall not be provided”—is that no reference may be made to the reference product’s dossier. Yet the EMEA guidelines that excuse biosimilars from certain safety tests or from efficacy tests for additional indications implicitly rely upon results from innovators’ data. Such reliance is extremely risky in the case of biologicals where there are always differences among various manufacturers’ products and “the process is the product, and the product is the process.” It needs to be recognized that the biosimilar situation is very different from the typical generic drug, a chemical that can be copied exactly, where the product is not so process-dependent and consistent copies can be produced through reverse engineering, good chemistry, tight specifications and GMPs.

VI. How does a product developer know what tests to do and what other steps to take?

This section of the report deals with:

- provision of scientific advice, a key function of the EMEA since its establishment in 1995 that was recently expanded;
- the “Article 58 process” in which a Scientific Opinion may be obtained from the CHMP, even if there is no interest in an EU marketing authorization; and
- fee reductions for small and medium-sized enterprises (SMEs).

A. The EMEA Scientific Advice Program

The EMEA finalized 257 scientific-advice, protocol-assistance and follow-up requests in 2006. As mentioned earlier, the EMEA received 79 initial marketing authorization applications in 2006. In 2005, 32% of applications for marketing authorization had been preceded by scientific advice requests. It is likely that the percentage has increased somewhat in 2006 and 2007 due to the

increased emphasis placed upon the scientific advice process and some improvements in its functioning.

In addition, there is much interaction between companies and Member State experts outside of the formal EMEA advice procedure. The EMEA wishes to enhance the usefulness of its scientific advice procedure and increase the proportion of applications that had been preceded by scientific advice requests to the EMEA. As a result available scientific advice has become more wide-ranging. However, the EMEA charges an initial request fee for scientific advice, while FDA advice is free. Moreover, follow-up requests for scientific advice can incur further fees. Fortunately, the EMEA eliminates or reduces fees in certain cases, such as for orphan drugs or products developed by companies identified as being SMEs.

The EMEA Regulation requires establishment of an administrative structure and procedures for development of advice for applicants. Advice on new therapies and indications on priorities. The Scientific Advice Working Party (SAWP) is a multidisciplinary group recently set up by the CHMP whose sole responsibility is the provision of scientific advice and protocol assistance to prospective applicants. ("Protocol assistance" applies to designated orphan medicinal products, under an EU Regulation on such products.) The SAWG's 26 members possess wide scientific expertise in preclinical safety, pharmacokinetics, statistics, cardiology, oncology, diabetes, neurodegenerative disorders and infectious diseases including HIV.

Scientific advice may be requested for all medicinal products for use in human beings, whether the products are eligible for the centralized procedure or not. Topics include guidance on the conduct of the various tests and trials to demonstrate the quality, safety and efficacy of new products. The EMEA advises that scientific advice requests and protocol assistance requests contain prospective questions concerning quality (chemical, pharmaceutical and biological testing), non-clinical (toxicological and pharmacological tests) and clinical aspects (studies in human subjects in either patients or healthy volunteers, including clinical pharmacological trials designed to determine the efficacy and safety of the product for pre or post-authorization activities) relating to the proposed future development of the product.

The SAWP also provides broader and more general advice for specific types of medicinal products or treatments and products intended for the mandatory centralized procedure introduced in the new EMEA Regulation. In such circumstances, advice can be provided in collaboration with the relevant Working Parties identified above. The SAWP can advise on whether medicinal products being developed for a specific therapeutic indication fulfill the criteria for optional participation in the central authorization procedure.

The SAWP will also consider requests for scientific advice concerning medicinal products intended to be marketed exclusively outside the EU, under Article 58 of the EMEA Regulation (discussed below on page 24).

Companies intending to submit requests for scientific advice can have pre-submission meetings prior to submission of such requests. Although these meetings are optional, they are strongly recommended, in particular for first time users of the advice procedures, and particularly for SMEs. Pre-submission meetings are an opportunity for applicants to introduce issues and to receive feedback from coordinators who are potential (EMEA staff members) on their proposed

development program for the product and the list of issues that need to be addressed. The meetings are a good opportunity for establishing contact with the EMEA coordinator and other EMEA staff who will be closely involved with the application as it proceeds. The pre-submission meeting also allows identification, at an earlier stage in the procedure, of both the types of studies and data needed and the additional expertise that needs to be involved.

A key aspect of the new scientific advice procedure is the effort to ensure systematic involvement in all types of advice, at the planning/pre-submission phase, of both the EMEA official serving as the applicant's coordinator and the assigned SAWG expert. It is hoped that this will, at least in some cases, lead to a reduction in the time taken to finalize certain types of scientific advice, to 40 days in some cases, up to a maximum of 70 days in others.

The plan for closer collaboration in the scientific-advice process with the CHMP and its Working Parties is a step in the right direction, although few details are available on how this process will work in practice. A feature of the scientific advice system that has tended to undermine its value was that the experts advising a future applicant at the scientific-advice stage may be entirely different from the rapporteur given the formal assignment by the CHMP of examining an application for authorization and reporting back on whether it ought to be authorized. This disconnect between advice and evaluation had led to skepticism about the value of the scientific review process, especially because there is a charge for the advice. Although the documents describing the new scientific advice process expressly state that the selection of the rapporteur for the assessment of the authorization remains a separate process, the promised collaboration between with SAWG and the CHMP suggests the likelihood of better coordination between the two phases of the EMEA process.

An important change that became effective in September 2006 was the adoption by CHMP of a new rapporteur selection policy (see the discussion on pages 8 and 9). Earlier, companies were able to include in their applications for marketing authorization a request as to which CHMP members they would like to see selected as rapporteur. Typically an applicant would give two or three names, and generally one of these would be named as rapporteur. In advance of their submissions, company representatives typically would have visited favored CHMP members in national capitals of EU Member States, both to obtain advice on clinical trial design and to try to gauge interest in the new product. The applicant's hope was that a favored CHMP member (one with solid expertise and an evident interest in the product) would volunteer to serve as that product application's rapporteur.

This change is aimed at addressing persistent imbalances in the assignment of rapporteur responsibilities among the Member States. CHMP members from the smaller States had some time complained that they were deprived from acting as rapporteur in the authorization of the "more interesting" products. Companies will no longer be able to indicate to EMEA their preferred candidates for rapporteurs. Now, the EMEA staff circulates to Member States advance lists of upcoming applications as they learn about them from future applicants. Also, before each CHMP meeting, the EMEA staff indicates in the agenda those products for which rapporteur responsibilities are to be assigned. Member States basically need to apply to the CHMP in writing to be assigned rapporteurship of an application, providing information on relevant scientific capability and product review experience. EMEA plainly wished to cease a process

which had been embarrassing for certain Member States, especially those whose service as rapporteur was seldom requested.

These changes also were hoped to channel more applicants' advice requests away from the Member States and into the revamped formal EMEA scientific advice process. It can be expected, however, that applicants will continue to seek ways to consult with experts in the competent authorities of the Member States, particularly those who are CHMP members or on the relevant Working Group or SAWP list, to obtain scientific advice or identify CHMP members who might want to apply to the EMEA to be rapporteurs. This is only to be expected since Member States remain the sole authorities approving and overseeing clinical trials and therefore get the first look at the clinical stage of those new products being tested in the EU.

B. Article 58 Scientific Opinions

The 2004 EMEA Regulation has created a means to obtain an expert Scientific Opinion from the well-respected CHMP, even if the product in question is not intended for marketing within the EU, and therefore is not in need of an EU marketing authorization.

The new EMEA Regulation acknowledges that many developing countries with limited regulatory capacity rely on prior assessment of a medicinal product by a developed country as an indicator for marketing suitability. However, many products needed by developing countries have no marketing authorization in a developed country. This may be the case where the disease that a medicine targets has no, or low, prevalence in developed countries and so development for developed countries' markets is not economically viable. The effort to facilitate access to these, often life-saving, medicines was partly responsible for the introduction of the Scientific Opinion procedure provided for in Article 58 of the revised EMEA Regulation.

This provision permits the EMEA to provide a Scientific Opinion, in the context of cooperation with the World Health Organization (WHO), for the evaluation of certain medicinal products for human use that are intended exclusively for markets outside the Community. Access to the Article 58 procedure is limited to those medicinal products perceived to be eligible for it. To be eligible, the product must be intended exclusively for markets outside the Community. It should also be intended to prevent or treat diseases of major public health interest. A non-exhaustive list of such products includes vaccines used, or of possible use, in the WHO Expanded Programme on Immunization (EPI); vaccines for protection against a WHO public health priority disease; vaccines that are part of a WHO managed stockpile for emergency response; and medicinal products for WHO target diseases such as HIV/AIDS, malaria, tuberculosis, lymphatic filariasis (elephantiasis), trachoma, leishmaniasis, schistosomiasis, African trypanosomiasis (sleeping sickness), onchocerciasis (river blindness), dengue fever, Chagas disease, leprosy. After having consulted with the WHO, EMEA will inform the applicant whether the product is eligible.

An application to the EMEA for a Scientific Opinion under Article 58 must conform to the usual, extensive requirements for an application for a centralized authorization. After consulting the WHO, the CHMP may draw up a Scientific Opinion in accordance with the EMEA Regulation. Nevertheless, Article 58 emphasizes that any medicinal product that is the subject of this Scientific Opinion process shall not, at the end of this procedure, be granted an EU authorization.

The Scientific Opinion provided by the CHMP on an application under Article 58 of the EMEA Regulation is considered to have equal standing to the opinions provided for medicinal products intended to be marketed in the EU. This is why the procedure mirrors the EU centralized procedure and why the information which the applicant provides is required to be so extensive. The evaluation is considered to be an EMEA/WHO partnership, with input from WHO experts and observers when this is needed. Moreover, observers from the WHO and from the authorities of developing countries may attend plenary discussions of the CHMP where these products are being considered.

Where the CHMP considers GMP, GCP or GLP inspections related to the medicinal product to be necessary for its evaluation and Scientific Opinion, it can require them. Inspections are coordinated by the EMEA but carried out by the competent authority inspectors. All recalls and defects that restrict supply are to be reported to competent authorities in the countries where the products are marketed.

The estimated time for completion of the CHMP Scientific Opinion under Article 58 is 210 days, excluding situations in which the clock stops to prepare responses by the applicant to the CHMP. The CHMP issues an EPAR, in coordination with WHO. This report contains the Committee's conclusions concerning the quality, safety and efficacy of the product and taking into account appropriate benefit/risk scenarios on populations and conditions of use as documents in the clinical data supplied by the applicant.

An example of the use of the Article 58 Scientific Opinion procedure was two antiretroviral products made by GSK for developing countries. The products are exact duplicates of EU-authorized products except as to product color; they are red rather than the usual white. The changed color is part of a program to assist the company and EU authorities in combating diversion back into the EU of exports intended for donation or reduced-price sales into developing countries. The procedure also was used for an Abbott antiretroviral.

There are undoubtedly advantages in having a Scientific Opinion based on Article 58 of the EMEA Regulation. However, taking account that the information that must accompany a request for such an Opinion is as extensive as that which must accompany a request for a centralized authorization, combined with the fact that the time limit within which the Opinion is to be given is the same as that for a marketing authorization and the fact that it is unclear to what extent fee reductions are available in the opinion procedure, a centralized authorization application would, potentially, be more beneficial to most applicants than a request for a Scientific Opinion.

C. Fees

The fees charged by the EMEA for the provision of the scientific advice, protocol assistance and follow-up requests are quite steep. SMEs are eligible for fee reductions, fee deferrals and conditional fee exemptions. This includes fee reductions for scientific advice, pre- and post authorization inspections, scientific services, and a full fee waiver for administrative services (with the exception of parallel distribution). There is also the possibility to defer payment of the fees payable for the application for marketing authorization and pre-authorization inspections,

and to receive a conditional fee exemption where scientific advice has been given and the application for marketing authorization is not successful (i.e., does not result in the grant of a marketing authorization). The reductions can be up to 100% of fees charged.

The reductions are available only to those companies that have been declared to be SMEs by the EMEA. Also, it should be noted that the SME must be established in the EU. This requirement can be satisfied by the formation of a corporate entity (or non-profit foundation) in one of the EU countries, although the documents on SME fee reductions set forth rules governing such transborder arrangements.

The initial request fee for scientific advice by EMEA is up to EUR 69,600, according to the EMEA Guidelines on Fees Payable and the Implementing Rules to which it is linked.

The EMEA charges EUR 52,200 for initial requests on clinical development and EUR 34,800 for initial requests on bioequivalence studies for generic medicinal products.

The fee for assessment of an application for marketing authorization (MAA) is as follows¹⁷:

Full Application:

EUR 232,000 basic fee (1 strength associated with 1 pharmaceutical form)

+ EUR 23,200 for each additional strength and/or pharmaceutical form

+ EUR 5,800 for each additional presentation of a strength and form (EMEA Guidelines on Fees Payable)

VII. How does the EU regulate GMPs?

All medicinal products for human use manufactured in or imported into the EU, including active pharmaceutical ingredients and medicinal products intended for use in clinical trials, are required to have been manufactured in accordance with GMP. Since 1991, this has been a requirement at the European Community level for marketed, finished dosage form medicinal products.

Recently EU authorities have ramped up regulatory activities in the area of GMPs. Some of these activities parallel efforts of the FDA to move toward a modern, risk-based, quality-management approach to GMPs, and recently the ICH initiated various GMP guideline projects aimed at ensuring that the EU and United States maintain congruent GMP regulatory systems.

Several of the EU documents on GMPs that are particularly important are:

- Commission Directive 2003/94/EC (October 8, 2003) on GMPs for both finished dosage form products and active starting materials;
- 2001 Clinical Trials Directive and 2005 GMP Directive extending GMPs to investigational medicines and other clinical trial material, i.e. placebos or active (the GMP Directive implements a provision in the Trials Directive detailed guidance be drawn up, in accordance with the guidelines on GMP, on elements to be taken into account when

evaluating Investigational medicinal products for human use with the object of releasing batches within the Community);

- Community Code Directive, which outlines GMP requirements and also requires Member States to license manufacturing facilities in their territories and to ensure that manufacturers follow GMPs;
- Guidelines for GMPs for medicinal products in general, active pharmaceutical ingredients, and for investigational products in the Notice to Applicants (NtA), as recently revised;
- Compilation of Community Procedures on Inspections and Exchange of Information.

The manufacturer shall ensure that manufacturing operations are carried out in accordance with GMPs and with the manufacturing authorization. This provision also applies to medicinal products intended only for export. For medicinal products and investigational medicinal products imported from non-EU countries, the importer shall ensure that products have been manufactured in accordance with standards at least equivalent to EU GMP standards.

The manufacturer shall ensure that all manufacturing operations for medicinal products subject to an authorization are carried out in accordance with the information in the application for marketing authorization as approved. For investigational medicinal products, the manufacturer shall ensure that all operations are carried out in accordance with sponsor information provided in the relevant clinical trial application as accepted by the relevant Member State drug regulatory agencies. Manufacturers shall regularly review production methods in the light of scientific progress and investigational product development. If a variation to the marketing authorization dossier, or an amendment to the clinical trial application is necessary, the application for modification shall be submitted to the relevant authorities.

The manufacturer shall establish and implement an effective pharmaceutical quality assurance system, involving active participation by management and personnel from different departments. At each production site, the manufacturer shall have a sufficient number of competent and appropriately qualified personnel available to achieve the pharmaceutical quality assurance objective.

Concerning quality control, the manufacturer shall establish and maintain a system placed under the authority of one person—the Qualified Person (QP)—who has the requisite qualifications and is independent of production. That person shall have, or have access to, one or more quality control laboratories, appropriately staffed and equipped to carry out necessary starting and packaging materials examination and testing, as well as the testing of intermediate and finished products. Contract laboratories may be used if authorised. However, under the Community Code Directive, there is the possibility that controls within the country where the medicinal product is manufactured can relieve the QP of certain responsibilities for recheck. For investigational medicinal products, the sponsor shall ensure that the contract laboratory complies with the clinical trial application's content, as accepted by the Competent Authority. When investigational medicinal products are imported from non-EU countries, analytical control is not mandatory.

A QP ensures that medicinal products (including investigational products) released into the EU have been produced under GMPs and meet other quality requirements.

For investigational medicinal products, the manufacturing process shall be validated in its entirety, as appropriate, taking into account the product development stage. At the least, critical process steps such as sterilization shall be validated. All steps in manufacturing process design and development shall be fully documented.

Contract manufacturing is also covered, and any manufacturing operation or operation linked thereto that is carried out under contract shall be the subject of a written contract that clearly defines each party's responsibilities and specifies, in particular, that GMPs must be followed. Provisions also are specified on complaints, product recall and records and reports. Any complaint concerning a defect shall be recorded and investigated by the manufacturer. The manufacturer shall inform the Competent Authority of any defect that could result in a recall or unusual restriction on supply and, insofar as is possible, indicate the countries of destination. These requirements apply at both the clinical trial and post-authorization stage.

EU and non-EU manufacturers whose products are to be used in the EU must follow GMP requirements. Even at the clinical trial stage, manufacturers and importers must have an EU-based QP who is responsible for ensuring that the products meet the specifications approved for the trial and have been made in accordance with existing EU GMP guidance. Member States may send investigators to visit sites involved in a clinical trial conducted to verify compliance with GCPs and GMPs.

Managerial and supervisory staff, including the QP, shall have duties defined in job descriptions and an organisation chart. Training and hygiene programs are required. There also are requirements for premises and equipment, documentation, validation, and quality control.

E. Requirements for wholesalers and distributors

The Community Code on Medicinal Products requires Member States to license wholesalers and distributors of medicinal products and to require observance by them of Good Distribution Practices (GDPs). To this end, the European Commission has published a Guideline on GDPs, with provisions resembling GMPs but focusing on responsibilities of the middlemen in the supply chain to maintain product quality. GDPs are particularly important in Europe due to the prevalence of parallel trade from countries where prices are lower to those with higher prices.

VIII. Conclusion

In sum, the EU has a robust regulatory system that rivals that of the United States in terms of its stringency and sheer complexity.

For further information, please contact Linda Horton at lrhorton@hhlaw.com

A. Case Study : The TeGenero Incident

A small German biotech company, Tegenero AG, was sponsor of a Phase I clinical study in Germany and the UK of a novel superagonist anti-CD28 monoclonal antibody that directly stimulates T cells. The company had completed the usual battery of preclinical toxicity tests. The company, the contract research organization (CRO) Parexel, the ethics committees, or two EU regulatory agencies that reviewed the clinical trial application (the UK MHRA and Germany's BfARM) saw no reason to foresee that the trial would be a problem.

Due to delays in the BfARM approval, no subjects in Germany received the product. However, in the UK, the MHRA approved the trial. Before the Clinical Trials Directive became effective in 2005, the MHRA did not even require sponsors to get its approval of Phase I clinical trials. When required by the Directive, change its procedures the MHRA had pledged to the drug industry that it would clear Phase I applications quickly, aiming at a 14-day turnaround.

So eight healthy male volunteers were recruited and dosed by Parexel Clinical Pharmacology Research Unit (CPRU) on March 13, 2006. Two subjects received a placebo. Serious adverse events (SAEs) were reported in six of the eight subjects:

- Within 90 minutes: systemic inflammatory response characterized by a rapid induction of proinflammatory cytokines and accompanied by headache, myalgias, nausea, diarrhea, erythema, vasodilatation, and hypotension;
- Within 12 to 16 hours: affected subjects were critically ill, with pulmonary infiltrates and lung injury, renal failure, and disseminated intravascular coagulation;
- Within 24 hours: severe and unexpected depletion of lymphocytes and monocytes; and
- At 8 and 16 days: intensive organ support was required in two patients due to prolonged cardiovascular shock and acute respiratory distress syndrome.

Despite this evidence of the multiple cytokine-release syndrome, all six patients survived.

Several reviews of the incident were carried out, with a focus on such issues as whether the reactions were due to contamination of the dose, an incorrect dose being administered, or an inherent flaw in the drug. Also there were queries about whether the short timeframe within which the doses were administered indicated poor clinical trial design.

An initial MHRA investigation found no errors in the manufacture, formulation, dilution or administration of TGN1412. An unpredicted biological action of the drug in humans was the most likely cause of the adverse reactions in the trial participants. The public was dissatisfied with the notion that everyone associated with the clinical trial, that resulted in such dramatic injuries was blameless. The MHRA then commissioned an investigation by an expert scientific group committee. It found that the preclinical development studies performed did not predict a safe dose in humans, even though current formal regulatory requirements were met. In addition, the German regulatory authorities conducted an inspection of the production facility and found no deficiencies in the manufacture, testing, storage and distribution of the TGN 1412 that could have contributed to the serious adverse effects.

A third UK review was carried out by an expert scientific group, which made a number of recommendations about Phase I clinical trials:

- Pre-clinical development:
 - Science-based decisions should be made and justified on a case-by-case basis by investigators with appropriate training.
 - There is need for strengthening the collection and sharing of information.
- Transition from preclinical to clinical development
 - A better approach to dose calculation is needed.
 - Goal should be maximum reduction of risk.
 - The starting dose and dose escalation should be made on a case-by-case basis and should be scientifically justifiable.
- Clinical development
 - A decision on whether to conduct a first-in-man trial should be carefully considered and fully justified.
 - Principal Investigators and staff should have appropriate levels of training, expertise, and qualifications.
 - Where there is a predictable risk of certain types of severe adverse reactions, a treatment strategy should be considered beforehand.

This year, the EMEA CHMP has developed a new guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products. This guideline, which is dated July 19, 2007, became effective on September 1, 2007. It:

- Identifies factors influencing risk for new investigational medicinal products
 - Predicting the potential severe adverse reactions for the first-in-man use of an investigational medicinal product involves identifying risk factors, which may in turn be derived from particular knowledge, or lack thereof, on:
 - mode of action; and/or
 - the nature of the target; and/or
 - the relevance of animal models;
- Considers quality aspects and in particular:
 - The determination of strength and potency, comparability with the material used, and reliability of very small doses;
- Considers non-clinical testing strategies and design for first-in-man clinical trials; and
- Suggests strategies for mitigating and managing risk, including calculation of the initial dose to be used in humans, subsequent dose escalation, and conduct of the clinical trial.

Member State agencies, including the MHRA and afssaps, also have issued guidelines on first-in-human clinical trials.

Because the payouts to the injured TeGenero volunteers under the clinical trial insurance were viewed by the public as rather modest, the TeGenero incident also highlighted the question of adequacy of insurance and provisions made for human subjects, particularly healthy volunteers. The issue of provisions for injured subjects was exacerbated by the fact that TeGenero went bankrupt. This led to many questions about what responsibilities (and legal liabilities) are borne not only by sponsors of clinical trials but also by CROs and regulators.

Notes

- ¹ <http://www.emea.europa.eu/htms/aboutus/emeaoverview.htm>
- ² Annual report of the European Medicines Agency 2005, EMEA/MB/63019/2006, at 14.
- ³ Directive 2001/20 of the European Parliament and of the Council.
- ⁴ 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, as amended.
- ⁵ Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.
- ⁶ EU institutions involved in lawmaking are the European Commission (which has the exclusive power to initiate the process), the European Parliament, and the European Council (top Member State officials).
- ⁷ Article 8.3(i)(b), Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating medicinal products for human use.
- ⁸ The Declaration of Helsinki is an international document published by the World Medical Association. It sets forth basic ethical principles for biomedical and clinical research in human subjects.
- ⁹ Commission Directive 2003/63 amending Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating medicinal products for human use.
- ¹⁰ Adopted by the EMEA Committee for Proprietary Medicinal products (CPMP) and issued as CPMP/ICH/2887/99 Rev. 2—Topic M4; Common Technical Document for the Registration of Pharmaceuticals for Human Use, 20 Nov. 2003.
- ¹¹ The summary of product characteristics is an important EU regulatory document that, among other things, defines what claims can be made about the product in marketing it to health professionals.
- ¹² http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-2/b/ctd_qa_05_2006.pdf
- ¹³ EMEA/CHMP/96268/2005.
- ¹⁴ CHMP Rapporteur/Co-Rapporteur appointment: principles, objective, criteria and methodology: <http://www.emea.europa.eu/pdfs/human/regaffair/12406605eu.pdf>
- ¹⁵ <http://www.emea.europa.eu/htms/human/presub/list.htm>
- ¹⁶ Article 10.6, Community Code.
- ¹⁷ EMEA Guidelines on Fees Payable.