



Harmonizing Pharmaceutical Regulation Among the United States, the European Union, and Japan: The ICH Initiative

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HARMONIZING PHARMACEUTICAL REGULATION AMONG THE UNITED STATES, THE EUROPEAN UNION, AND JAPAN

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Abstract:

The United States, the European Union and Japan comprise 75% of the world's pharmaceutical market and generate 90% of all pharmaceutical research. Recognizing the need for and benefits of harmonized testing standards the United States, the European Union and Japan formed a joint initiative between the industry and regulators called the International Conference on Harmonization (ICH). The ICH initiative has been underway for over a decade now. This paper will examine the disparate pharmaceutical regulatory regimes of the U.S., the EU, and Japan and will explore the ICH effort and its progress thus far.

Part I of this paper overviews the current regulation of new pharmaceuticals in the United States, the European Union, and Japan. Based on these overviews, it will be apparent that the regulatory agencies of these three regions have already made some progress in harmonizing international standards. Part II explores the forces at work behind harmonization and discusses the potential benefits of pharmaceutical harmonization. Part III explains the ICH initiative including the mechanics of the ICH process and its implementation in the three ICH regions. Part IV of the paper addresses problems inherent in, and barriers to the achievement of the goals of the ICH. Finally, Part V of the paper discusses the accomplishments of the ICH thus far and evaluates its impact on the drug review process.

INTRODUCTION

Drug regulatory agencies share the common goal of allowing safe and effective drugs to reach the market. Despite this, drug regulators have acted in isolation in developing standards for evaluating the quality, safety and efficacy of drugs. Accordingly, the detailed technical requirements of drug testing standards have varied significantly from country to country. As a result of this, new drugs poised for international marketing have been subject to multiple and duplicate testing. The time and costs associated with this multiple testing and unnecessary regulation have been overwhelming.¹ This results in higher prices, delays in treatment and the unavailability of some drugs in some markets.² Harmonization of the scientific requirements of pharmaceutical regulatory schemes worldwide will reduce duplication of tests and speed the approval of drugs throughout the world.

¹David W. Jordan, *International Regulatory Harmonization: A New Era in Prescription Drug Approval*, 25 VAND. J. TRANSNAT'L L. 471, 491 (1992).

²Ileana Dominguez-Urban, *Harmonization in the Regulation of Pharmaceutical Research and Human Rights: The Need to Think Globally*, 30 CORNELL INT'L L.J. 245, 245 (1997).

The United States, the European Union and Japan comprise 75% of the world's pharmaceutical market and generate 90% of all pharmaceutical research.³ Recognizing the need for and benefits of harmonized testing standards the United States, the European Union and Japan formed a joint initiative between the industry and regulators called the International Conference on Harmonization (ICH).⁴ The ICH initiative has been underway for over a decade now. This paper will examine the disparate pharmaceutical regulatory regimes of the U.S., the EU, and Japan and will explore the ICH effort and its progress thus far.

Part I of this paper overviews the current regulation of new pharmaceuticals in the United States, the European Union, and Japan. Based on these overviews, it will be apparent that the regulatory agencies of these three regions have already made some progress in harmonizing international standards. Part II explores the forces at work behind harmonization and discusses the potential benefits of pharmaceutical harmonization. Part III explains the ICH initiative including the mechanics of the ICH process and its implementation in the three ICH regions. Part IV of the paper addresses problems inherent in, and barriers to the achievement of the goals of the ICH. Finally, Part V of the paper discusses the accomplishments of the ICH thus far and evaluates its impact on the drug review process.

I. CURRENT REGULATION OF PHARMACEUTICAL PRODUCTS

A. The United States

1. Overview: The FDA and the Food Drug and Cosmetic Act

³Rosemarie Kanusky, Pharmaceutical Harmonization: Standardizing Regulations Among the United States, The European Economic Community, and Japan, 16 HOUS. J. INT'L L. 665, 667 (1994).

⁴Alessandra Cortez, Introducing the International Conference on Harmonization Guidelines Into the World Trade Organization: A Strategy to Remove Technical Trade Barriers for Pharmaceutical Products, The International Commercial Diplomacy Project, at http://www.commercialdiplomacy.org/ma_projects/cortez.htm (Spring 2002).

“The sale and distribution of pharmaceuticals in the United States is primarily controlled by the Food, Drug, and Cosmetic Act, which is interpreted and enforced by the Food and Drug Administration (FDA).”⁵ The regulatory and scientific body that oversees the development and marketing of all new drugs is the FDA’s Center for Drug Evaluation and Research (CDER).⁶

The FDA oversees what is generally regarded as the world’s most demanding drug regulation and approval process.⁷ In the past, critics of the FDA have asserted that the rigors and inefficiencies of the FDA’s review process for new drugs have resulted in fewer, and the delayed availability of, new drugs.⁸ However, a good deal has changed in the past decade to accelerate the speed with which the FDA approves new drugs.⁹

Much of the FDA drug review process has been reformed under the Food and Drug Administration Modernization Act of 1997 (FDAMA) and the reauthorized Prescription Drug User Fee Act (PDUFA).¹⁰ “[W]hat made FDAMA particularly significant was its new philosophical approach, which redefined and broadened FDA’s original character as a self-reliant public health law enforcement agency.”¹¹ Prior to the enactment of FDAMA, the FDA’s mission was focused primarily on the following overall objectives: “1) a timely review of regulated products, 2) the protection of public health by ensuring that food and cosmetics are safe and properly labeled, 3) ensuring that human and veterinary drugs are safe and effective, 4) providing a reasonable assurance of the safety and effectiveness of medical devices, and 5) public protection from electronic product radiation.”¹²

FDAMA added two additional objectives to the FDA’s mission: to “participate... with representatives in

⁵Kanusky, *supra* note 3, at 668.

⁶MARK MATHIEU, NEW DRUG APPROVAL IN THE UNITED STATES 64 (2002/2003 ed., PAREXEL International Corporation 2002).

⁷*Id.* at 1.

⁸Jordan, *supra* note 1, at 471.

⁹Mathieu, *supra* note 6, at 1.

¹⁰Mathieu, *supra* note 6, at 63.

¹¹Linda A. Suydam & Milan J. Kubic, *FDA’s Implementation of FDAMA: An Interim Balance Sheet*, 56 FOOD & DRUG L.J. 131, 131 (2001).

¹²*Id.*

other countries to reduce the burden of regulation, harmonize regulatory requirements, and achieve appropriate reciprocal agreements;” and to “carry out [its mission] in consultation with experts... and in cooperation with consumers, users, manufacturers, importers, packers, distributors, and retailers of regulated products.”¹³

Additionally, in 1997, the Prescription Drug User Fee Act (PDUFA I) of 1992 was reauthorized for another 5 years (PDUFA II).¹⁴ Under PDUFA I, the FDA had agreed to meet accelerating time frames for reviewing certain human drugs and biological products in return for fees paid by drug manufacturers.¹⁵

In addition to shorter time frames under PDUFA II, the FDA has agreed to a new set of procedural goals intended to enhance the quality and efficacy of the drug development process. These goals included “specifying time-limits for such activities as scheduling technical guidance and pre-submission meetings with the product sponsors, resolution of major disputes and clinical holds, and rapid handling of other procedural, processing and management issues.”¹⁶ PDUFA I and PDUFA II have been extremely successful, with the FDA meeting or exceeding nearly all of their performance goals. The median total approval time for new drug applications has decreased from 23.8 months in 1990 to 11.6 months by the end of 1999. Median approval time of priority applications has dropped from over 13 months in 1990 to 6 months by 1999.¹⁷ Due to their tremendous success, negotiations are underway to put PDUFA III into effect in September 2003.¹⁸ The current evolutionary phase of new drug regulation in the United States is being driven by a focus on international harmonization and risk management.¹⁹ The following are examples of changes that have been set in motion by this focus. By August 2001, the ICH’s Common Technical Document (CTD) format be-

¹³Id.

¹⁴Id. at 133.

¹⁵Id. at 133.

¹⁶Id. at 133.

¹⁷Id. at 133.

¹⁸Note that the FDA’s approval of large number of new drug in record time has not gone without criticism. The agency faced considerable criticism after three approved drugs (Redux, Posicor, and Duract) were withdrawn from the market in 1997 and 1998. The primary criticism was that the agency’s focus on speed of approval came at the expense of drug safety. Mathieu, *supra* note 6, at 1.

¹⁹Mathieu, *supra* note 6, at 1.

came a regulatory option to the NDA for companies seeking FDA approval of a new drug.²⁰ Additionally, in response to concerns regarding drug safety, the CDER has integrated “risk management” considerations into NDA reviews.²¹ In doing so, the CDER is asking drug sponsors and its reviewers what additional steps can be taken to make a newly approved drug as safe as possible in the marketplace. Risk management alternatives that the CDER is evaluating more and more in new drug reviews include restricted distribution programs, educational programs, patient package inserts, special surveillance systems, and safety-related communications.²² Finally, in acknowledgement that in the face of speedier and rising numbers of drug approvals there is a need for a particularly well-conceived post-marketing drug surveillance program, CDER officials announced a reinvigorated post-marketing drug surveillance program under a newly named Office of Post-Marketing Drug Risk Assessment (OPDRA).²³ Nevertheless, while several factors have influenced U.S. drug approval in recent years, the fundamentals of the new drug approval process remain intact within the provisions of the Food, Drug and Cosmetic Act (FD&C Act).²⁴

2. New Drug Development and the Drug Approval Process

a) Pre-clinical Testing

“Because of the costs and risks inherent in using an untested drug in clinical testing, [...] drug sponsors do not leap headlong into a clinical program once they have identified a promising compound.”²⁵ Before beginning clinical testing, a drug sponsor must provide information demonstrating that “the company can manufacture the drug, descriptions of the proposed clinical trials, and data establishing that the drug is

²⁰Mathieu, *supra* note 6, at 1.

²¹Mathieu, *supra* note 6, at 2.

²²Mathieu, *supra* note 6, at 2.

²³Mathieu, *supra* note 6, at 2.

²⁴Mathieu, *supra* note 6, at 3.

²⁵Mathieu, *supra* note 6, at 5.

reasonably safe for use in initial, small-scale, clinical studies.”²⁶ Depending on whether the compound has been studied or marketed previously, there may be several alternative ways for accomplishing this last requirement. The sponsor may: (1) compile existing non-clinical data derived from past *in vitro* or animal studies on the compound; (2) compile data from previous clinical testing or marketing of the drug in the U.S. or another country whose population is similar to that of the United States; or (3) undertake new pre-clinical studies.²⁷

For drugs whose clinical safety and efficacy have not been established in the past, the first major step towards regulatory approval is pre-clinical *in vitro* and *in vivo* animal testing.²⁸ From the pre-clinical stage, the FDA requires that sponsors develop a pharmacological profile of the drug, determine the acute toxicity of the drug in at least two species of animals, and conduct short-term toxicity studies whose duration is based on the duration of the proposed clinical studies.²⁹

Because pre-clinical drug development does not involve human exposure to an experimental compound, drug developers have considerable flexibility in manufacturing, shipping, and testing experimental drugs.³⁰ Practically the only regulatory limitation facing sponsors conducting pre-clinical studies are the general animal welfare provisions in current federal and state animal protection statutes and regulations and the FDA requirement that in order to ship a drug intended solely for tests *in vitro* or in animals used only for laboratory research purposes be labeled as follows: “Caution: Contains a new drug for investigational use only in laboratory research animals, or for tests *in vitro*. Not for use in humans.”³¹

When a drug sponsor is compiling safety data that it will submit to the FDA, the Good Laboratory Practice

²⁶Mathieu, *supra* note 6, at 5.

²⁷Mathieu, *supra* note 6, at 5.

²⁸Mathieu, *supra* note 6, at 5.

²⁹Mathieu, *supra* note 6, at 5.

³⁰Mathieu, *supra* note 6, at 5.

³¹Mathieu, *supra* note 6, at 6.

(GLP) regulations apply. The FDA requires the use of GLP standards to ensure the quality of animal testing and of the data in which it results.³²

b) The IND Application and FDA Review of the IND

When a drug sponsor deems that it has adequate data that demonstrates that the new drug has a high degree of promise in treating a particular disease and is sufficiently safe for initial small-scale clinical trials, the sponsor assembles and submits an Investigational New Drug (IND) application to the FDA.³³ The NDA is the means by which the drug sponsor obtains an exemption from the statutory requirement that bans the shipment of unapproved drugs in interstate commerce.³⁴

In the IND, the sponsor reports: (1) the results of pre-clinical testing and an analysis of the implications of these results for human pharmacology; (2) an analysis of the drug's chemical composition and the quality control procedures used in producing the compound; and (3) protocols explaining the drug sponsor's plans for the initial-stage clinical studies proposed in the IND, and information describing the relevant qualifications of the investigators who will carry out these studies.³⁵

Upon submitting the IND application, the sponsor must wait 30 days to allow the FDA to review the application. The FDA's review of an IND involves:

³²Mathieu, *supra* note 6, at 6.

³³Mathieu, *supra* note 6, at 6.

³⁴Mathieu, *supra* note 6, at 6.

³⁵In an attempt to stop the wave of Phase I studies moving to European nations (resulting from the impression that European countries generally have less demanding standards for initial stage clinical research), in November of 1995, the FDA "clarified" its IND content requirements. "Specifically, the agency established its willingness to accept toxicology data summaries and line listings based upon sponsors' unaudited draft toxicological reports of completing animal studies in INDs for Phase 1 studies. By accepting these summaries and listings based on unaudited draft reports, and permitting companies to update this information 120 days after trials are initiated, the FDA, in effect, permits sponsors to begin phase 1 trials months earlier than in the past." Mathieu, *supra* note 6, at 6.



Pharmacology/Toxicology Review—The results of the animal pharmacology and toxicity data are reviewed by a pharmacologist who attempts to relate these results to human pharmacology.

♣ Chemistry Review—The sponsor’s manufacturing processes and control procedures are evaluated by a chemist to make certain that the compound is reproducible and in its pure form. Additionally, the chemist compares the drug’s characterization, chemical structure, and impurity profile to that of other drugs known to be toxic.

♣ Clinical Review—Clinical protocols are evaluated by a reviewing medical officer (generally a physician) to make sure that test subjects will not be exposed to unreasonable risks during the clinical trials, and that Phase 2 and Phase 3 trials are satisfactory in design.³⁶

If the FDA determines that certain clinical trials may not commence, “the agency contacts the sponsor within the 30-day period to initiate what is called a “clinical hold”—the delay of the clinical trial until potential problems of unanswered questions are addressed.”³⁷ If the FDA does not respond to the applicant within 30 days, the sponsor may begin clinical trials pursuant to the standards set forth in the IND application and FDA regulations.³⁸ Thus, the agency does not literally approve an IND, but allows clinical testing to begin through its “administrative silence.”³⁹

c) Clinical Trials

Clinical trials embody the most critical and demanding phase in the drug development process. “If a drug

³⁶Mathieu, *supra* note 6, at 7.

³⁷Mathieu, *supra* note 6, at 7.

³⁸Jordan, *supra* note 1, at 479.

³⁹Mathieu, *supra* note 6, at 7.

survives the rigors of clinical testing, the FDA's ultimate approval decision will be based primarily upon data derived from these studies.”⁴⁰

The rise in clinical development times was the dominant regulatory controversy of the mid-1990s. The industry maintained that the relentless rise in clinical development times was extremely prohibitive.⁴¹ This, along with changes in the competitive environment for pharmaceuticals, helped to accelerate several trends, including industry efforts to streamline their clinical development programs and to enhance their clinical trial efforts internationally. This reality may also have been a motivation behind a new FDA initiative to better define the clinical trial data required for drug approval.⁴² In an attempt to assist sponsors, in May of 1998, the FDA released guidance entitled, *Providing Clinical Evidence for Human Drug and Biological Products*, which supplied the agency's latest views on the “quantitative and qualitative” standards for establishing drug effectiveness.⁴³

Clinical trials for different drugs are usually similar in structure. “Since researchers may know little about a new compound prior to its use in humans, testing the drug through serially conducted studies permits each phase of clinical development to be carefully designed to use and build upon the information obtained from the research phase preceding it.”⁴⁴ Clinical investigations most often proceed in three phases.

Phase 1 begins with initial tests of the new drug on normal human volunteers. Low doses of the drug are administered to 20 to 80 subjects.⁴⁵ The purpose of this phase is to determine the drug's toxicity, and obtain other pharmacological information.⁴⁶

⁴⁰Mathieu, *supra* note 6, at 7.

⁴¹Mathieu, *supra* note 6, at 7.

⁴²Mathieu, *supra* note 6, at 7.

⁴³Mathieu, *supra* note 6, at 8.

⁴⁴Mathieu, *supra* note 6, at 8.

⁴⁵Mathieu, *supra* note 6, at 8.

⁴⁶Jordan, *supra* note 1, at 480. (Phase I allows the sponsor to evaluate the drug's pharmacology and pharmacokinetics, mechanism of action in humans, side effects (of various doses), the optimal route of administration, and the safe dosage range) Mathieu, *supra* note 6, at 8.

Phase II is essentially an extension of Phase I, except in this phase the primary consideration is whether the drug is effective.⁴⁷ Clinicians conduct controlled studies on 100 to 200 patients who suffer from the condition that the drug is intended to treat. In addition to providing indication of the drug's effectiveness in its projected use, it provides additional safety data. Furthermore, the results of phase II studies can determine the foundation for chief aspects of phase III study design.⁴⁸

Next is Phase III. Not only is phase III the longest and most extensive phase of clinical testing, but it is also the most time consuming part of the entire drug approval process. The purpose of Phase III is to "study the circumstances under which physicians prescribe the drug for their patients."⁴⁹ This phase will only commence if the data from the previous two phases provides sufficient assurance that the drug is safe and effective and that the potential benefits of the drug outweigh the potential risks of a larger clinical trial.⁵⁰ Phase III involves the use of the drug on an appreciably larger groups of patients (several hundred to several thousand) who suffer from the condition that the drug is intended to treat. Because some of the Phase III trials (known as "pivotal" trials) will serve as the primary basis for the drug's approval, these studies have to meet more exacting standards.⁵¹

d) The New Drug Application

Upon successful completion of the IND process, the sponsor typically files a New Drug Application (NDA).⁵² "Since 1938, the new drug application has been the vehicle through which drug sponsors formally propose that the FDA approve a new pharmaceutical for sale and marketing in the United States."⁵³ NDAs generally

⁴⁷Jordan, *supra* note 1, at 480.

⁴⁸Mathieu, *supra* note 6, at 8.

⁴⁹Jordan, *supra* note 1, at 480.

⁵⁰Jordan, *supra* note 1, at 480.

⁵¹Mathieu, *supra* note 6, at 8.

⁵²Jordan, *supra* note 1, at 481.

⁵³Mathieu, *supra* note 6, at 8.

consist of thousands of pages of clinical and non-clinical data and analysis derived from “adequate tests by all methods reasonable applicable.”⁵⁴

However, in August 2001, the ICH produced the Common Technical Document (CTD).⁵⁵ This now provides another option for companies seeking FDA approval to market new drugs in the U.S. During the “transition period,” which will last until July 2003, companies have the choice of submitting U.S. marketing dossiers in either the CTD or the NDA format.⁵⁶ Starting July 2003, the FDA will highly recommend that U.S. marketing dossiers be submitted in CTD format.⁵⁷ The FDA, however, will not be able to make this a formal requirement until it undertakes a comprehensive revision of its NDA regulations.⁵⁸ It is noteworthy that while the CTD may differ from the NDA in format, it does not differ in content. Furthermore, the submission standards needed to obtain FDA approval will also not be affected by the move to the CTD format.⁵⁹

Regardless of which format is used, the FDA marketing dossier for a new drug is extensive. The application must provide an exhaustive review of essentially all of the information the sponsor possesses about the drug. The agency reviewers need to have sufficient data and information to make numerous key determinations, including: “(1) whether the drug is safe and effective in its proposed use(s), and whether the benefits of the drug outweigh its risks; (2) whether the methods used in manufacturing the drug and the controls used to maintain the product’s quality are adequate to preserve its identity, strength, and purity; and (3) whether the drug’s proposed labeling is appropriate and, if not, what the drug’s labeling should contain.”⁶⁰

Additionally, the CDER has expanded its technical infrastructure such that it can accept electronic NDAs

⁵⁴Jordan, *supra* note 1, at 481.

⁵⁵Mathieu, *supra* note 6, at 9.

⁵⁶Mathieu, *supra* note 6, at 9.

⁵⁷Mathieu, *supra* note 6, at 9.

⁵⁸Mathieu, *supra* note 6, at 9.

⁵⁹Mathieu, *supra* note 6, at 9.

⁶⁰Mathieu, *supra* note 6, at 9.

(e-NDAs). The Pharmaceutical industry appears to be embracing the concept of electronic NDAs. Of the sixty-one NDAs filed in FY2001, 35% were electronic submissions.⁶¹

e) The NDA Review Process

The NDA review process has evolved more over the past ten years than any other element of the drug approval system. “So fundamental were these changes-and the improvements in drug review times that resulted from them-that CDERs NDA review performance was transformed from one of the most harshly criticized of FDA activities into what was perhaps the agency’s best defense against regulatory reform proposals advanced in the mid-1990s.”⁶²

The motivating forces behind this development were PDUFA I and II, and the changes that the CDER put into practice in order to meet the new review timelines associated with this PDUFA legislation.⁶³ The CDER introduced tight controls for managing and tracking drug reviews. Additionally, the CDER’s review divisions were organized into smaller, more therapeutically focused units.⁶⁴

Once an NDA is submitted, it is passed on to one of CDER’s drug review divisions—specifically the CDER drug review division that manages the therapeutic area applicable to the submission.⁶⁵ Within 45 days of the NDA’s submissions, FDA reviewers meet to determine whether the application is complete.⁶⁶ If the application is sufficiently complete, the NDA is “filed,” or in other words, accepted for review. If the reviewers find that the application is deficient, then the FDA files a refuse-to-file (RTF) decision and the application

⁶¹Mathieu, *supra* note 6, at 9.

⁶²Mathieu, *supra* note 6, at 175.

⁶³Mathieu, *supra* note 6, at 9.

⁶⁴Mathieu, *supra* note 6, at 9.

⁶⁵Mathieu, *supra* note 6, at 10.

⁶⁶Mathieu, *supra* note 6, at 10.

is returned to the sponsor.⁶⁷

Upon the filing of an application, the review team starts the “primary review” of the application. During this evaluation, each member of the review team sifts through volumes of research data and information applicable to his or her expertise.⁶⁸ Additionally, the filing decision prompts a division request that FDA field office to undertake an inspection of the sponsor’s manufacturing facilities.

Once the primary reviews are completed, each reviewer prepares a written evaluation presenting her conclusions and recommendations concerning the NDA. Generally the medical reviewer then evaluates and reconciles the conclusions of the reviewers from the other scientific disciplines.⁶⁹

“For NDA’s submitted in FY1998 through FY 2002, the FDA must review performance goals associated with PDUFA II. The new review goals will differ for ‘priority’ drugs (i.e., drugs representing a significant improvement over market products) and “standard” drugs. A six-month review timeframe will apply to priority applications during PDUFA II, while the agency has agreed to take action on increasing percentages of standard applications within 10 months.”⁷⁰

Upon completion of the review, the CDER issues an action letter (an approval or not-approval letter) which conveys the results of the review to the applicant. Additionally, it may identify issues or defects that must be addressed before the application can be approved. Under PDUFA, the CDER has committed to developing a regulation establishing that a new type of action letter, called a “complete response” letter, will replace the approval and non-approval letters.⁷¹

3) Acceptance of Foreign Data

⁶⁷Mathieu, *supra* note 6, at 10.

⁶⁸Mathieu, *supra* note 6, at 10.

⁶⁹Mathieu, *supra* note 6, at 11.

⁷⁰Mathieu, *supra* note 6, at 11.

⁷¹Mathieu, *supra* note 6, at 11.

Traditionally, the FDA has had a strong bias against accepting foreign data. Recently, however, they have started accepting non-U.S. clinical data and have recently approved new chemical entities based on trials conducted exclusively outside of the United States.⁷²

B. The European Union

1. Background

a) The Path to a Unified Europe

Following WWII, a number of European nations came to believe in the need for a more integrated Europe. In 1957, six states (Belgium, France, Germany, Italy, Luxembourg, and the Netherlands) signed the Treaty of Rome, thereby establishing the European Community (EC). Since then, the Community has grown and the organization now known as the European Union (EU) currently consists of 15 states: Austria, Belgium, Denmark, Ireland, Finland, France, Germany, Greece, Italy, Luxembourg, the Netherlands, Portugal, Spain, Sweden and the United Kingdom.⁷³ Considering the desire of other nations to join the EU, the number of member states is likely to grow.

Since its establishment, the EU's goal has been the creation of a fully integrated internal market through the removal of all barriers to the free movement of goods, persons, services and capital.⁷⁴

⁷²Elizabeth M. Rutherford, *The FDA and Privatization—The Drug Approval Process*, 50 FOOD & DRUG L.J. 203 203, 222 (1995).

⁷³MONICA LOFGREN & MIA DREESSEN, NEW DRUG APPROVAL IN THE EUROPEAN UNION 3 (PAREXEL International Corporation 2002/2003 ed. 2002).

⁷⁴*Id.*

b) The Road to the EMEA

“From the European Community’s early days, the national pharmaceutical marketing authorization procedures within the individual Member States constituted a barrier to the free movement of medicinal products due to differences in procedures, data requirements, standards and the time taken to reach decisions on applications.”⁷⁵ In an effort to eliminate these barriers, European Community Directives were adopted to institute: “(t)he requirements for pharmaceutical product marketing authorization; (t)he Committee for Proprietary Medicinal Products (CPMP), consisting of experts from each of the national regulatory agencies; and (t)he multistate procedure, a non-mandatory process for the mutual recognition of pharmaceutical product licenses issued by the individual national agencies.”⁷⁶

The hope was that once a company received marketing authorization in one of the European Community countries, the other member states would recognize this approval and license the product in their respective countries. “In the unlikely event of disagreement, the case could be referred to the CPMP for a final decision. In reality, however, almost every case using this multistate procedure was referred to the CPMP, whose decision was not binding on the Member States.”⁷⁷ In 1987, an additional procedure known as the “concertation procedure” was introduced. Its introduction reflected the European Community’s conviction that the efficient development and registration of such products was vital to the success of the European Pharmaceutical industry. While somewhat more successful than the multistate procedure, it had the same essential problem—specifically the lack of a binding decision. This meant that companies had to negotiate with each Member State for a national license.⁷⁸

⁷⁵*Id.*

⁷⁶*Id.* at 4.

⁷⁷*Id.* at 4.

⁷⁸*Id.* at 4.

Due to the deficiencies of these procedures and lack of progress achieved by assorted legislation that had been passed, a period of extensive deliberation followed. The result of such deliberation was the creation of the European Agency for the Evaluation of Medicinal Products. A new CPMP along with two new procedures—the centralized procedure and the mutual recognition (decentralized) procedure—were incorporated.⁷⁹

2. Regulatory Agencies

a) The EMEA

The introduction of Europe's centralized drug approval procedure required the creation of a new European Agency—the European Agency for the Evaluation of Medicinal products. This agency, generally referred to as the European Medicines Evaluation Agency (EMA), or the Agency, began functioning in February 1995.⁸⁰ The EMA's primary responsibilities concern the administration of the centralized procedure.⁸¹ While the EMA does not have a direct role in the technical reviews of the centralized applications, it hosts the CPMP, which provides the scientific opinions on centralized applications based on the reviews of assigned experts.⁸² The Agency is also in charge of pharmacovigilance⁸³ and Good Manufacturing Practice (GMP) inspections.⁸⁴ Unless an application is referred to it for arbitration, the EMA is not involved in the mutual recognition procedures.

The EMA consists of the following four primary entities: 1) a management board; 2) an executive director;

⁷⁹*Id.* at 4.

⁸⁰*Id.* at 5.

⁸¹*Id.* at 18.

⁸²*Id.* at 19.

⁸³Pharmacovigilance is the process of collecting information on adverse drug reactions at the pre and post-marketing stages, scientifically evaluating these adverse drug reaction reports, and making the regulatory decisions that result from this analysis. REPORT TO THE CHAIRMAN, COMMITTEE ON LABOR AND HUMAN RESOURCES, U.S. SENATE., U page 23.

⁸⁴Lofgren & Dreessen, *supra* note 73, at 18.

3) a permanent secretariat; and 4) three scientific committees together with their working parties—the Committee for Proprietary Medicinal Products (CPMP), the Committee for Veterinary Medicinal Products (CVMP), and the Committee for Orphan Medicinal Products (COMP).⁸⁵ The Management Board consists of representatives from all 15-member states, the European Commission, and the European Parliament.⁸⁶ It is the governing body of the EMEA and is responsible for budgetary matters and for ensuring co-ordination of the national resources of the member states.⁸⁷ An executive director heads the Agency, and the Permanent Secretariat is the administrative center that provides general and logistical support to the scientific committed and for the day-to-day administration of the EMEA.⁸⁸

The job of the CPMP and the CVMP is to evaluate the scientific data presented by pharmaceutical companies and to issue opinions regarding the approvability and labeling of products. Moreover, since the beginning of the millennium, the EMEA has hosted the Committee for Orphan Medicinal Products (COMP). This committee is responsible for determining whether drugs should be conferred orphan drug status.⁸⁹

The majority of the EMEA's funding is derived from user fees. Presently, 70% of the EMEA's funding is obtained from user fees and another 24% is provided from the EU budget. Today, user fees include not only application-associated fees but also an annual fee and a fee for the scientific advice procedure as well.⁹⁰

⁸⁵Lofgren & Dreessen, *supra* note 73, at 19.

⁸⁶Lofgren & Dreessen, *supra* note 73, at 5.

⁸⁷Lofgren & Dreessen, *supra* note 73, at 20.

⁸⁸Lofgren & Dreessen, *supra* note 73, at 19.

⁸⁹Lofgren & Dreessen, *supra* note 73, at 5.

⁹⁰Lofgren & Dreessen, *supra* note 73, at 5.

b) The CPMP

From an applicant's point of view, the EMEA's Committee for Proprietary Medicinal Products (CPMP) is the EMEA's most important body because it provides the agency's objective, scientific opinion upon which the European Community bases its decision on each product application.⁹¹

"The EMEA's Committee for Proprietary Medicinal Products (CPMP) consists of two members from each member state; these members are elected to renewable three-year terms. The CPMP selects its chairman from its membership during a closed session."⁹² On the basis of scientific measures for quality, efficacy, and safety, an opinion is issued by the CPMP on the approvability of marketing applications submitted under the centralized procedure. Based on this opinion, the European Commission decides whether to issue a license for the product. For each centralized application, the CPMP assigns a rapporteur and often times also a co-rapporteur from its membership. In addition, the committee appoints rapporteurs for arbitration cases referred to it under the mutual recognition procedure. Rapporteurs are also assigned by the CPMP for arbitration cases referred to it because of differences in national decisions and for cases in which the interest of the Community is concerned.⁹³

The actual evaluation of marketing dossiers is performed by experts who are chosen by the rapporteur. These experts are selected from an approved list of European experts who are either on the staff of the national agencies or are "external" European experts. While the CPMP attempts to reach a scientific consensus among its members, a majority opinion is sufficient when a unanimous decision is not possible. All decisions subsequently formulated from this CPMP opinion (e.g., a drug's authorization) are binding on all Member States.⁹⁴

The CPMP has created several working groups to assist it with its work. Because of the increased number of applications requiring review and the increased complexities of the issues being considered, more of the

⁹¹Lofgren & Dreessen, *supra* note 73, at 22.

⁹²Lofgren & Dreessen, *supra* note 73, at 6.

⁹³Lofgren & Dreessen, *supra* note 73, at 7.

⁹⁴Lofgren & Dreessen, *supra* note 73, at 7.

CPMP’s workload is being delegated to these working parties. Ultimately, however, the full CPMP must consider and reach a decision on each issue.⁹⁵

A procedure growing in significance is the scientific advice procedure. This procedure allows companies to seek the CMPC’s advice during a product’s development, for a fee. In order to handle this process, the CMPC has formed an informal CPMP working group called the Scientific Advice Review Group. While this group is currently an informal working group, it is likely to be organized as one of the CPMP’s Working Parties in the future. Additionally, more emphasis will likely be placed on the pre-submission phase in order to help companies develop their products and submit higher quality applications.⁹⁶

c) The European Commission

Traditionally, the European Commission is described as performing the following three functions: initiating proposals for legislation; serving as the guardian of the Treaties; and executing EU policies and actions, including the pharmaceutical decision-making process.⁹⁷

“All opinions formed and issued by the EMEA’s CPMP—including decisions to authorize new drugs under the centralized approval process—must be converted into decisions that are binding on all Member States.”⁹⁸ Because the CPMP does not have the authority to make binding decisions, the European Commission is necessary in order to take action to make their decisions binding. With the help of a body called the Standing Committee (which consists of representatives from all of the Member States), the European Commission adopts final CPMP opinions. When there is serious dissent between the Member States regarding such

⁹⁵Lofgren & Dreessen, *supra* note 73, at 7.

⁹⁶Lofgren & Dreessen, *supra* note 73, at 7.

⁹⁷Lofgren & Dreessen, *supra* note 73, at 31.

⁹⁸Lofgren & Dreessen, *supra* note 73, at 30.

opinions, the EU’s Council of Ministers becomes involved.⁹⁹ All binding decisions follow a specific procedure called the decision-making process, outlined in Regulation (EEC) 2309/93 and in Regulation 1662/95.¹⁰⁰

d) National Agencies

“[T]he national agencies throughout Europe continue to play the major role in all matters relating to the mutual recognition procedure.” The EMEA is only involved in the procedure when an application is referred to it for arbitration. Moreover, the national agencies continue to register products when the national routes must be used, such as for line extensions when the first application was approved through the old national routes and for applications for local generic product.¹⁰¹

Furthermore, the national agencies accept responsibility for the maintenance of all products approved and on the market before the new European Regulatory became effective. Additionally, the Reference Member State agency is in charge of reviewing new data to sustain marketed products approved through the Mutual Recognition procedure or the centralized procedure. Finally, the national agencies supply the majority of the experts engaged in reviewing applications submitted under the centralized route.¹⁰²

3. Registration Procedures

⁹⁹Lofgren & Dreessen, *supra* note 73, at 30.

¹⁰⁰Lofgren & Dreessen, *supra* note 73, at 96.

¹⁰¹Lofgren & Dreessen, *supra* note 73, at 43.

¹⁰²Lofgren & Dreessen, *supra* note 73, at 43.

a) The Centralized Procedure

Under the centralized procedure, a single application, a single evaluation administered by the EMEA, and a single authorization provide direct and simultaneous access to the EU's 15 Member States. Additionally, Iceland and Norway have been participating in the centralized process since January 2000.¹⁰³ The Annex to Council Regulation 2309/93 established that two classes of medicinal products could contend for the centralized procedure.¹⁰⁴ Products listed in Part A of the Annex must be registered through the centralized procedure even if marketing of the product is intended in only one member state. On the other hand, sponsors of Products in Part B have the option of using either the centralized process or the mutual recognition process.¹⁰⁵

Evidence thus far strongly suggests that the pharmaceutical industry is embracing the centralized procedure. By the end of the year 2000, 279 applications had been submitted to the EMEA via the centralized procedure. Of these 279 applications, only one-third involved Part A products (products for which the centralization procedure is mandatory). Such statistics reveal that drug companies were choosing to use the centralized procedure for products for which it was not required.¹⁰⁶

Part A products are all biotechnology products developed through any of the following processes: "recombinant DNA technology; controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes, including transformed mammalian cells; hybridoma and monoclonal antibody methods."¹⁰⁷

Part B includes a number of innovative products, such as new medicinal products derived from human blood or human plasma, and medicinal products administered by means of a new delivery system which in the opinion of the agency constitute a significant innovation.¹⁰⁸

¹⁰³Lofgren & Dreessen, *supra* note 73, at 67.

¹⁰⁴Lofgren & Dreessen, *supra* note 73, at 69.

¹⁰⁵Lofgren & Dreessen, *supra* note 73, at 69.

¹⁰⁶Lofgren & Dreessen, *supra* note 73, at 5.

¹⁰⁷Lofgren & Dreessen, *supra* note 73, at 69.

¹⁰⁸Lofgren & Dreessen, *supra* note 73, at 69.

A rapporteur is the scientific project leader selected by the CPMP for a given application in the centralized process. A rapporteur is generally not the primary reviewer for an application but instead serves to organize the review. The CPMP normally selects both a rapporteur and a co-rapporteur so as to provide for two independent reviews of an application. Experts whom the rapporteur selects from a list of accepted European experts perform the actual scientific review.¹⁰⁹

Since the introduction of the centralized procedure, companies by and large have been granted at least one of their preferences for rapporteur or co-rapporteur. Due to the increase in the number of requests for rapporteurs from the same subgroup of Member States and the CPMP's partiality towards the even distribution of work among all of the CPMP Member States in rotation, fulfilling application requests has been more difficult.¹¹⁰ This, along with the requirement that a single common drug name be used in all of the 15 Member States and Iceland and Norway, are two limitations associated with the centralized process.¹¹¹

Under the centralized procedure, scientific assessment of the application should take no more than 120 days. At that point, the review clock stops to allow the applicant to respond to a list of CPMP questions. Additionally, the CPMP will notify the applicant whether the file is approvable or non-approvable. The CPMP will then give the company a chance to supply the necessary information and specified data. Although the legislation does not specify the duration of this clock stop, the CPMP expects that the clock stop will not exceed 6 months.¹¹²

Following the CPMP's review of the additional information supplied in response to its questions and comments, the CPMP determines whether there are still unresolved issues.¹¹³ "When necessary, the committee may invite the company to a hearing at the EMEA's London offices in hopes of reaching a resolution for

¹⁰⁹Lofgren & Dreessen, *supra* note 73, at 77.

¹¹⁰Lofgren & Dreessen, *supra* note 73, at 8.

¹¹¹Lofgren & Dreessen, *supra* note 73, at 70.

¹¹²Lofgren & Dreessen, *supra* note 73, at 8.

¹¹³Lofgren & Dreessen, *supra* note 73, at 8.

pending issues.”¹¹⁴ Such a hearing takes place by Day 180 after which the CPMP reaches a preliminary opinion. The committee’s final opinion on an application will be issued by day 210, when all of the administrative paper work must be finalized. The CPMP’s opinion must subsequently be submitted to the European Commission in order for the decision to be made legally binding.¹¹⁵

b) The Mutual Recognition Procedure

Under the new mutual recognition procedure, the national recognition of a product in one Member State may be “mutually recognized” by another Member State following a specific request by the applicant and the submission of an identical file to the Member States where the applicant wants to market its product.¹¹⁶ If the other Member States mutually acknowledge the first approval with or without negotiation, then the CPMP is not drawn into the procedure. If any of the Member States involved fail to mutually recognize the product’s original authorization within 90 days, then the case is referred to the CPMP for arbitration, unless the applicant withdraws the application in the objecting Member State(s). At a standard CPMP meeting, the committee discusses the pending application and selects a rapporteur for the arbitration process. Additionally, experts may be appointed from the list of approved European experts to prepare a further assessment report. The final recommendation of the CPMP in arbitration cases is binding on all the Member States involved in a specific mutual recognition procedure.¹¹⁷

Unlike the centralized procedure, the mutual recognition procedure has not been very successful. Problems have arisen primarily from the mutual recognition procedure’s “lack of ownership—that is, no single group

¹¹⁴Lofgren & Dreessen, *supra* note 73, at 9.

¹¹⁵Lofgren & Dreessen, *supra* note 73, at 9.

¹¹⁶Lofgren & Dreessen, *supra* note 73, at 9.

¹¹⁷Lofgren & Dreessen, *supra* note 73, at 9.

among all the players involved in the process is accountable for its success or failure.”¹¹⁸ Notwithstanding the fact that completed review and assessment reports are available from the Reference Member State (the country that first approves the drug), a majority of the Member States nevertheless conduct their own independent application reviews under the mutual recognition procedure and raise countless questions for applicants. To provide Member States a chance to resolve issues among themselves, procedures have been set up through which Member States that are in conflict can meet with the Reference Member State to attempt to settle the unresolved issues. A voluntary group named the Mutual Recognition Facilitation Group has been formed to discuss issues concerning mutual recognition and to offer “break-out” sessions during which Member States concerned can discuss problems associated with a specific application. Applicants also may be invited to take part in such meetings.¹¹⁹

C. Japan

Considerable changes have taken place in Japan’s drug approval process since the late 1990s. The most significant of these changes include “the creation of the new Ministry of Health, Labor and Welfare (MHLW), the streamlining of the Japanese NDA review process, Japan’s growing acceptance of foreign-generated clinical data, and the country’s implementation of several harmonized ICH guidelines that affect both non-clinical and clinical activities.”¹²⁰ With such changes Japan has evidenced a desire to make its process more consistent with those of the world’s other major markets and a desire to eliminate many of the impediments for new drug development and approval within its country.¹²¹

¹¹⁸Lofgren & Dreessen, *supra* note 73, at 10.

¹¹⁹Lofgren & Dreessen, *supra* note 73, at 10.

¹²⁰KEITH B. RUSSELL & W. MICHAEL BREMER, NEW DRUG APPROVAL IN JAPAN 1 (PAREXEL International Corporation, 2002/2003 ed. 2002).

¹²¹*Id.*

1. Japanese Regulatory Authorities

a) The Ministry of Health, Labor and Welfare (MHLW)

The Japanese drug regulatory body is known as the Ministry of Health, Labor and Welfare (MHLW), or the Koseisho.¹²² In addition to being responsible for pharmaceutical regulation in Japan, the MHLW is responsible for the advancement of social welfare, social security and the public health.¹²³ Of the MHLW's eleven bureaus, the main "MHLW bureaus responsible for pharmaceutical regulation are the Pharmaceutical and Medical Safety Bureau (PMSB), the National Institutes of Health Sciences' Pharmaceutical and Medical Devices Evaluation Center (PMDEC), and the Organization of Pharmaceutical Safety and Research (OPSR/KIKO)."¹²⁴

b) Pharmaceutical and Medical Safety Bureau (PMSB)

The PMSB plays the role of the leader of the Ministry's drug evaluation and safety functions. Two of the PMSB's most significant units are the Evaluation and Licensing division and the Safety Division.¹²⁵ The Evaluation and Licensing division is responsible for "the review and approval of manufacturing, re-examination, and re-evaluation applications."¹²⁶ The key role of the Safety Division is to amass adverse drug reaction data and make certain the adequacy of the Japanese government's measures aimed to protect patient safety.¹²⁷

¹²²The Koseisho was formed in the January 2001 merger of Japan's Ministry of Health and Welfare and Japan's Ministry of Labor. *Id.*

¹²³*Id.*

¹²⁴*Id.* at 3.

¹²⁵*Id.* at 4.

¹²⁶*Id.* at 5.

¹²⁷*Id.* at 6.

c) The Health Policy Bureau

The Office of Industry Research and the Research and Development Division of the Health Policy Bureau are the Ministry's two primary offices relating to the drug approval process. The Research and Development Division offers guidance for and supervision of the KIKO concerning basic research, the promotion of research, and the promotion of orphan drug development.¹²⁸ "The Office of Industry Research collects and publishes information on pharmaceutical companies and the entire pharmaceutical industry (and related companies), and supports the drafting of industrial policies by the Health Policy Bureau."¹²⁹ Additionally, it functions as a forum for discussion of information and opinions through consultations with the industry.¹³⁰ According to Japanese law as of April 1, 2000, anybody has the right to request disclosure of documents held by national governmental agencies. As a result of this law, the MHLW must release the contents of its reviews (new drug approval information dossiers, etc.). Companies commencing clinical development activities in Japan are encouraged to obtain as much relevant information to their development program as they can through this office.¹³¹

d) The National Institute of Health Sciences' Pharmaceuticals and Medical Devices Evaluation Center

The National Institute of Health Sciences (NIHS)¹³² oversees the Pharmaceuticals and Medical Devices Evaluation Center (PMDEC). Furthermore, the NIHS carries out tests and research on drugs, quasi-drugs, cosmetics, medical devices, food, poisons, and powerful drugs. "The institute is responsible for the reexam-

¹²⁸*Id.* at 7.

¹²⁹*Id.* at 7.

¹³⁰*Id.* at 7.

¹³¹*Id.* at 8.

¹³²The National Institute of Health Sciences was formerly known as the National Institute of Hygienic Sciences. *Id.* at 8.

ination and reevaluation of approved drugs and medical devices.”¹³³

e) Pharmaceuticals and Medical Devices Evaluation Center (Evaluation Center)

Established in 1997, the Pharmaceuticals and Medical Devices Evaluation Center (PMDEC) plays the main role in the drug review and approval process. “It is responsible for conducting the reviews required for approving the manufacturing o(f) import drugs, quasi drugs, cosmetics and medical devices and for conducting the re-examination and re-evaluation of drugs and medical devices.”¹³⁴ Additionally, it is in charge of accelerating and improving the expertise accessible for new drug review drugs and for the general strengthening of the review system.¹³⁵

The Evaluation Center consists of 5 main divisions, four of which are therapeutic area-specific evaluation divisions that are responsible for conducting NDA reviews and for re-examining and re-evaluating approved drugs. The following are the Evaluation Center’s divisions: The Planning and Coordination division, which consists of the office of General Affairs and the Office of Information; Division I, which handles antibiotics, chemotherapeutics and anti-cancer drugs; Division II, which handles cardiovascular drugs, anti-allergic drugs and urogenital drugs; Division III which handles biological products, blood products, radio-pharmaceuticals, generic prescription drug products, over-the-counter drugs, quasi drugs an cosmetics; and Division IV which handles *in vitro* diagnostics and medical devices.¹³⁶

¹³³*Id.* at 8.

¹³⁴*Id.* at 8.

¹³⁵*Id.* at 8.

¹³⁶*Id.* at 8.

f) The Organization for Pharmaceutical Safety and Research (KIKO)

The Organization for Pharmaceutical Safety and Research is also known as the KIKO, meaning “Drug Organization.” The KIKO is responsible for administering the Adverse Drug Reporting (ADR) Relief Law and for monitoring industry compliance with Good Laboratory Practice (GLP) Provisions and Good Clinical Practice (GCP) Standards. Additionally, the KIKO provides assistance to companies in the designing of orphan drug development programs.¹³⁷

When conducting GLP compliance inspections, the KIKO usually asks for the assistance of the appropriate regional Prefectural Office. Approximately two or three GLP inspections per year are performed outside of Japan, in countries with which Japan does not have a reciprocal GLP agreement.¹³⁸

Beginning in April 1997, the KIKO began offering fee-based consultation services for the planning and conduct of clinical studies. Furthermore, they reviewed clinical study protocols and the validity of data attached to the pharmaceutical marketing authorization applications.¹³⁹ All documents generated during these communications are attached to the New Drug Application and will be considered part of the application.¹⁴⁰

While drug sponsors are advised to meet with the KIKO as early as possible in order to receive its input on the development plan before significant time and resources have been invested in it, the fee charged by the KIKO is extremely high¹⁴¹ and it does not ensure that the MHLW will approve the new drug.¹⁴²

¹³⁷ *Id.* at 9.

¹³⁸ *Id.* at 9.

¹³⁹ *Id.* at 9.

¹⁴⁰ *Id.* at 10.

¹⁴¹ The KIKO’s fee has been reported to be as high as \$25,000 US dollars an hour. *Id.* at 10.

¹⁴² *Id.* at 10.

2. Japan's Drug Development and Approval Process

a) Pre-clinical testing:

As in the United States and the EU, the safety of new clinical studies to be conducted in Japan must be backed by animal toxicology studies before they are initiated.¹⁴³ For many years, the required pre-clinical studies have been based on *Japan's Guidelines for Toxicity Studies Required for Applications for Approval to Manufacture or Import Drugs*.¹⁴⁴ As a result of the ICH initiative, however, Japanese authorities have modified many of their own non-clinical testing requirements and guidelines to harmonize them with new non-clinical, or safety, guidelines released by the ICH. In other cases, ICH guidelines have replaced Japanese guidance documents completely.¹⁴⁵

“Based upon ICH agreements implemented to date, the non-clinical studies necessary to support initial and subsequent clinical studies on Japan include single dose toxicity studies, repeated dose toxicity studies, reproductive and developmental studies, genotoxicity studies, skin sensitization studies, and skin photosensitization studies. For drugs that present special concerns or are intended for a long duration of use, a sponsor must assess carcinogenic (carcinogenicity studies) potential. Typically, however, carcinogenicity studies need not be completed prior to the drug's first exposure to man. The recommended duration of the repeated dose toxicity studies usually is related to the drug's indication and proposed duration of use, as well as the scale of the proposed clinical trial.”¹⁴⁶

The primary objective of non-clinical safety studies is to provide sufficient information to support the selection of the initial human dose and the safe duration of exposure in initial clinical studies. These studies

¹⁴³*Id.* at 10.

¹⁴⁴Notification No. 718, dated February 15, 1984, subsequent revisions on September 1989 and November 1999. *Id.* at 11.

¹⁴⁵*Id.* at 17.

¹⁴⁶*Id.* at 12.

should also make available information about the experimental drug's physiology and toxicological effects.¹⁴⁷ Additionally, this data will assist in preventing and understanding adverse events in clinical trials.¹⁴⁸ Regardless of the country in which the pre-clinical studies are performed, particular key safety studies must comply with Good Laboratory Practice (GLP) standards.¹⁴⁹ For those studies to which GLP applies, the pre-clinical testing facilities will be subject to GLP compliance inspections.¹⁵⁰ The KIKO conducts these reviews after an application is submitted. Based upon their findings, a facility will receive one of three ratings:

- 1) Class A: Compliance with GLP
- 2) Class B: Some improvements are possible, but the effects of non-compliance on the data's reliability are not considered significant (improvements are encouraged)
- 3) Class C: Non-compliance with GLP¹⁵¹

The MHLW will accept the test results and use them in the pending application review if the testing facility receives a Class A or Class B rating.¹⁵² Japan's GLP requirements also apply to non-clinical data generated in foreign countries. Mutual acceptance of GLP inspection results and data from several countries is provided through the bilateral agreements. Countries with such bilateral agreements with Japan include Switzerland, the United Kingdom, Germany, France, Holland and Sweden.¹⁵³

b) Clinical Trial Notification:

¹⁴⁷ *Id.* at 17.

¹⁴⁸ *Id.* at 12.

¹⁴⁹ *Id.* at 12.

¹⁵⁰ *Id.* at 26.

¹⁵¹ *Id.* at 12.

¹⁵² *Id.* at 27.

¹⁵³ *Id.* at 27.

Once satisfactory animal and *in vitro* data has been collected and analyzed, the drug developers must file a Clinical Trial Notification (CTN) with the MHLW before commencing human clinical trials. Rather than a formal request for government approval, the CTN is a notification. In spite of this, the drug developer cannot initiate the studies put forward in the CTN until 30 days after the regional Prefectural Office receives the CTN. Moreover, before initiating the studies, the drug developer must resolve any significant questions that arise during the Koseisho's review.¹⁵⁴

The conventional CTN is a brief document addressing the following areas:



“Ingredients and quantities of the trial drug;



Method of manufacturing for the trial drug, including test results;



Anticipated indications and effects of the trial drug;



Anticipated dose and route of administration of the trial drug;



Purpose, design, and period of the trial;



In cases in which the trial sponsor is not domiciled in Japan, the name and address of the in-country caretaker;



Name and address of each institution involved in the trial, the names of the physicians responsible for performing the trial, and the anticipated amount of the trial drug can be delivered (the drug must be delivered

¹⁵⁴ “Initiation” is defined as the shipment of drugs to the investigational unit. *Id.* at 29.

directly to each institution by the sponsor, and the exact amount and date of delivery must be recorded); and

♣ A justification for any fee charged for the clinical trial drug.¹⁵⁵

c) Clinical Trials in Japan

Clinical trials must conform to Japan's Good Clinical Practice (GCP) standards.¹⁵⁶ These standards were revised in April of 1997. Prior to 1997, the clinical trials were dominated by physician-investigators.¹⁵⁷ Under this system, the sponsor's role was limited to providing clinical trials support, administration, and data analysis. Similarly, Japan's regulatory agencies provided only administrative reviews of development programs and a final sign off on scientific reviews.¹⁵⁸ Furthermore, pre-1997 clinical trials often employed "soft" endpoints based on physician implemented and subjective scales of efficacy, safety, and usefulness.¹⁵⁹ "During the 1990s, Japan's drug development system evolved considerably—from an idiosyncratic system unique to Japan to a more harmonized and ICH-compatible system."¹⁶⁰ Under the April 1997 revisions, virtually all of the elements of the ICH-promulgated GCP standards were incorporated into Japan's drug development system.¹⁶¹

d) The Japanese NDA

A drug is defined as a "new" drug if "at the time of application for a manufacturing or import approval, it is designated as different (e.g., by virtue of an active ingredient's chemical structure the desired indication,

¹⁵⁵*Id.* at 30.

¹⁵⁶*Id.* at 12.

¹⁵⁷*Id.* at 41.

¹⁵⁸*Id.* at 42.

¹⁵⁹*Id.* at 42.

¹⁶⁰*Id.* at 41.

¹⁶¹*Id.* at 43.

or the planned dosage form) from those already approved in Japan.”¹⁶²

In advance to marketing a new drug in Japan, a sponsor must submit and obtain government approval for a new drug application (NDA) and either a manufacturing plant license, if the drug is to be manufactured in Japan, or an import license. Like the United States and Europe, Japan evaluates its NDAs based on the drug’s quality, safety and efficacy.¹⁶³ A typical Japanese NDA contains the following:

- 1) Outline of data submitted
- 2) Application form
- 3) Proposed packet insert
- 4) Copies of certificates (primarily compliance statements)
- 5) Application Summary (including appendices for specific listing of study information)
- 6) List of data submitted
- 7) Data
- 8) Other references as necessary¹⁶⁴

The most important scientific requirement in the Japanese NDA is the Application Summary, also known as Gaiyo (synopsis). It functions as the chief application reference throughout the government’s review.¹⁶⁵ The Gaiya should concisely sum up the main points pertaining to the quality, safety, and efficacy of the drug, and these points must be based on, and referenced back to the documents appended to the application.¹⁶⁶ ICH efforts, however, are bringing about significant changes to marketing dossiers in Japan. “Like the United States and the European Union, Japan has agreed to accept marketing dossiers in the harmonized

¹⁶²*Id.* at 63.

¹⁶³*Id.* at 13.

¹⁶⁴*Id.* at 15.

¹⁶⁵*Id.* at 70.

¹⁶⁶*Id.* at 70.

common technical document (CTD) format.” Up until July 2003, Japan will be going through a transitional period. Up until that time, applicants seeking drug approval in Japan will have the choice of submitting their marketing dossiers in the regular Japanese NDS format or under the CTD format. After July 1, 2003, however, Japan will require that the CTD format be used in all applications.¹⁶⁷

e) The NDA Review Process

The NDA review process begins when the applicant submits an NDA to the pharmaceutical section of the local Prefectural Government Office. For foreign companies, this would be the office responsible for the district in which the company’s in-country caretaker is located. Upon receiving an NDA, the local Prefectural Government Office ensures that all of the required documents are included in the submission. After the company addresses any issues raised during this administrative review, the local Prefectural Government Office then submits the application to the Pharmaceuticals and Medical Devices Evaluation Center (PMDEC).¹⁶⁸ The Evaluation Center then forwards the application’s clinical and non-clinical data files to the KIKO, which reviews the data’s reliability and ensures that the studies producing the data complied with GCP and GLP requirements. Once the KIKO validates the reliability of the data and the studies, the Evaluation Center begins its review of the new drug’s efficacy, safety, and quality.¹⁶⁹

As of November 2000, the evaluation process put into practice by the PMDEC involves the following steps:

1) An interview involving a sponsor presentation, queries and data checks; 2) A team review involving meetings with members of KIKO and advisory experts; 3) An additional interview with further inquiries and data checks; 4) An Initial report is issued; 5) A specialists meeting with at least three clinical experts; 6) A hearing allowing the applicant to discuss any issues with the reviewers and specialists; 7) A follow up

¹⁶⁷*Id.* at 63.

¹⁶⁸*Id.* at 97.

¹⁶⁹*Id.* at 98.

specialists meeting; 8) A second report is issued; and finally 9) A second report is forwarded to the PMSB's Evaluation and Licensing Division.¹⁷⁰

Following this process, a report is submitted to the Pharmaceutical Affairs Section of the PAFSC for review. Subsequent to this review, the report is forwarded to the MHLW, where the Minister grants the new drug approval.¹⁷¹ At this point, the MHLW prepares a New Drug Approval Information Package (NAIP) based on the review data. The NAIP is published so as to ensure that accurate information obtained during the review process involving the efficacy, quality and safety and that is required for the proper use of the drug, can be supplied to medical professionals and medical institutions.¹⁷²

While no official mechanism exists for a sponsor to appeal the Japanese government's refusal to approve a license to manufacture, sell or import a drug,¹⁷³ the applicant may request that the MHLW reevaluate the usefulness and necessity of the product.¹⁷⁴ The drug company may supply new analysis of the already submitted data, but may not submit new data. Consequently, the chance of success for a previously rejected application is poor.¹⁷⁵

3) Acceptance of Foreign Data

Japan's stance on the employment of foreign clinical data to support new drug approvals has changed substantially over the past few years. In 1998, Pharmaceutical Affairs Bureau (PAB) Notification No. 660 (June 1985) was supplanted by Notification 739 on the utilization of foreign clinical data, and Notification

¹⁷⁰*Id.* at 13.

¹⁷¹*Id.* at 13.

¹⁷²*Id.* at 101.

¹⁷³*Id.* at 103.

¹⁷⁴*Id.* at 104.

¹⁷⁵*Id.* at 104.

672 on the bearing of ethnic factors on the acceptability of foreign data. Under Notification 660, only safety data derived from foreign clinical trials could be employed to back approval in Japanese NDAs, while efficacy and clinical pharmacology data could be received only as supportive, non-pivotal data for a product's registration. However, according to the latest notifications (Notifications 672 and 739), which are based on ICH guidelines, data from foreign clinical trials can be used, provided that they: (1) are found to have resulted from studies compliant with Japanese GCP standards; and (2) the drug's effects are not likely to be affected by ethnic factors. If it is considered necessary as a result of this review, the sponsor will conduct a study, called a "bridging study," to show whether the study results in non-Japanese subjects can be extrapolated to the Japanese population. If it can be so extrapolated, the foreign data will be accepted in the Japanese NDA.¹⁷⁶

The fact that the MHLW's is willing to allow foreign data in NDAs signifies a notable change in Japan's drug development system. Currently, a number of drug development programs have, through the KIKO consultation process, requested the assessment of their plans to include foreign data in a Japanese NDA.¹⁷⁷ Many of these companies are preparing to conduct bridging studies. One obstacle in this new environment is that Japanese regulators or investigators have not put forth a clear definition of what constitutes a bridging study forward. Applicants therefore should consult with the KIKO regarding their plans.¹⁷⁸

¹⁷⁶ *Id.* at 55.

¹⁷⁷ *Id.* at 55.

¹⁷⁸ *Id.* at 56.

II. HISTORY OF PHARMACEUTICAL HARMONISATION

1. Early History of Harmonization

Since 1965, the European Economic Community (EEC), now the European Union, has sought to harmonize pharmaceutical regulation. By 1975, the EEC had established the Committee for Proprietary Medicinal Products (CPMP). The aim of the CPMP was, and continues to be, to “facilitate the adoption of a common position by individual licensing authorities.”¹⁷⁹ By 1985, the EEC had instituted a timetable for the elimination of obstacles to pharmaceutical trade within the community.¹⁸⁰ Concurrently, the EEC began bilateral discussions on possible pharmaceutical harmonization with both Japan and the United States.¹⁸¹ It was not until 1989, at the WHO Conference of Drug Regulatory Authorities (ICDRA) in Paris, that all three parties convened together to make specific plans for trilateral harmonization.¹⁸² In April 1989, at a meeting hosted by the European Federation of Pharmaceutical Industries and Associations in Brussels, the ICH was formed.¹⁸³ ICH headquarters was later set up in Geneva, Switzerland, with the International Federation of Pharmaceutical Manufacturers Association taking over administrative duties for the ICH.¹⁸⁴

2. Forces Behind Harmonization

“The urgent need to rationalize and harmonize regulation was impelled by concerns over rising costs of

¹⁷⁹Joseph G. Contrera, *The Food and Drug Administration and the International conference on Harmonization: How Harmonious Will International Pharmaceutical Regulations Become?*, 8 ADMIN. L.J. AM. U. 927, 939 (1995).

¹⁸⁰*Id.*

¹⁸¹Alessandra Cortez, *Introducing the International Conference on Harmonization Guidelines Into the World Trade Organization: A Strategy to Remove Technical Trade Barriers for Pharmaceutical Products*, The International Commercial Diplomacy Project, at http://www.commercialdiplomacy.org/ma_projects/cortez.htm (Spring 2002).

¹⁸²International Federation of Pharmaceutical Manufacturers Associations, *ICH Past and Future*, International Conference on Harmonisation, at <http://www.ich.org/ich8.html>.

¹⁸³Alessandra Cortez, *Introducing the International Conference on Harmonization Guidelines Into the World Trade Organization: A Strategy to Remove Technical Trade Barriers for Pharmaceutical Products*, The International Commercial Diplomacy Project, at http://www.commercialdiplomacy.org/ma_projects/cortez.htm (Spring 2002).

¹⁸⁴*Id.*

health care, escalation of the cost of R&D and the need to meet the public expectation that there should be a minimum of delay in making safe and efficacious new treatments available to patients in need.”¹⁸⁵ The governments of several European countries and the United States were experiencing increasing consumer demands for improved access to new drugs.¹⁸⁶ The FDA in particular, was under continual pressure both from inside and outside the agency to be more efficient¹⁸⁷

In addition to the continual pressure for greater efficiency in the drug approval process, several other major forces are at work behind international drug harmonization as envisioned by these three regions. The increasingly international character of products and industries that the FDA regulated,¹⁸⁸ the need for better global market access for Japanese pharmaceutical products,¹⁸⁹ economic globalization and a growing economic interdependence between the regions have also been forces behind the move toward harmonization.¹⁹⁰ Moreover, provisions of the World Trade Organization agreements such as the Agreement on the Application of Sanitary and Phytosanitary Measures and the Agreement on Technical Barriers to Trade, encourage harmonization.¹⁹¹

An additional force behind the movement towards international pharmaceutical harmonization is a borderless Europe under the EU.¹⁹² The move towards a borderless Europe may also serve to explain the reason for the FDA’s support of the ICH. “Once commentator recently queried whether FDA’s participation in ICH is due, at least in part, to a fear of losing its stature as the world’s preeminent regulatory body for drug approval.”¹⁹³ The FDA has always held itself out as the “gold standard” in this respect largely because of

¹⁸⁵International Federation of Pharmaceutical Manufacturers Associations, *ICH Past and Future*, International Conference on Harmonisation, at <http://www.ich.org/ich8.html>.

¹⁸⁶David V. Eakin, *The International Conference on Harmonization of Pharmaceutical Regulations: Process or Stagnation?*, 6 TULSA J. COMP. & INT’L L. 221, 221 (1999).

¹⁸⁷Dan Kidd, *The International Conference on Harmonization of Pharmaceutical Regulations, The European Medicines Evaluation Agency, and the FDA: Who’s Zooming Who?*, 4 IND. J. GLOBAL LEGAL STUD. 183, 184 (1996).

¹⁸⁸Linda Horton, *Mutual Recognition Agreements and Harmonization*, 29 SETON HALL L. REV. 692, 693 (1998).

¹⁸⁹Russell & Bremer, *supra* note 120, at 42.

¹⁹⁰Krzysztof Kuik, *Recent Developments in EU/US Trade Relations*, 79 U. DET. MERCY L. REV. 433, 435 (2002).

¹⁹¹Horton, *supra* note 188, at 694.

¹⁹²Dan Kidd, *The International Conference on Harmonization of Pharmaceutical Regulations, The European Medicines Evaluation Agency, and the FDA: Who’s Zooming Who?*, 4 IND. J. GLOBAL LEGAL STUD. 183, 184 (1996).

¹⁹³Paul M. Booth, *FDA Implementation of Standards Developed by the International Conference on Harmonisation*, 52

its authority over the largest equivalently regulated market for pharmaceuticals. The size of the U.S. market ensured that drug manufacturers would establish development and testing programs around the demands of U.S. regulators. “In this light, FDA assumed that harmonization meant, in essence, conformity to the U.S. model. For many years this was true, and Europe and Japan followed the United States’ lead.¹⁹⁴ The EMEA, however, now oversees a consistent regulatory system over a significantly larger population than that of the U.S. This creates the possibility of the EMEA displacing the FDA as the de facto regulatory standard setting agency for drug approval.¹⁹⁵

3. Potential Benefits from Pharmaceutical Harmonization

There are numerous potential benefits to the pharmaceutical industry that could result from harmonization.

a) Timesaving

Perhaps the strongest impact of harmonization will be the resultant saving of time. Inconsistent national standards create lag time between product development and distribution thereby increasing industry costs including loss of sales, loss of revenue from a decrease in effective patient life, loss of working capital, and loss of staff costs for processing multiple applications. Such timesavings will provide earlier access to innovative therapies. This will help save more lives and will also be more profitable to companies.¹⁹⁶

b) A Reduction in the Cost of Drug Development

FOOD & DRUG L.J. 203, 207 (1997).

¹⁹⁴ *Id.*

¹⁹⁵ *Id.*

¹⁹⁶ Jordan, *supra* note 1, at 497.

Harmonization will allow drug companies to avoid duplicative tests in states that are parties to the ICH agreement. Furthermore, it will simplify preparation of application dossiers¹⁹⁷ and will lessen the costs associated with guiding drugs through the process of regulatory review for each country's market. This will provide companies with great cost savings. These savings in costs will be beneficial for the drug companies and consumers.¹⁹⁸ Companies will be able to shift these cost savings into more research and development of new drugs.¹⁹⁹ Consumers will benefit from the development of new drugs. Furthermore, as the cost of drug approval declines, more pharmaceutical companies may enter the market, which will increase competition among drug companies and could result in a decline in drug prices. In addition, it will allow smaller drug companies to enter the market. Multinational companies bear extremely large expenses in learning the various regulations of each market in which they operate. "This capital-intensive process eliminates small drug companies" from the development of new drugs.²⁰⁰

c) Improvement of World Health

Harmonization will ideally make the world safer, and thereby reduce the spread of disease within and between nations. Health concerns of nations are interrelated. Most developing countries use a certification scheme, which allows use of the drug if it has been approved for use in the nation that developed it.²⁰¹ Hence, they are relying on the regulatory processes of the developed countries. The certification scheme is problematic when drugs are received from nations whose regulatory process is too lax (because dangerous and ineffective drugs could be marketed). If pharmaceutical regulation is harmonized such that the regulatory processes of developed nations ensure the efficacy and safety of drugs, the developing nations will be better off.

¹⁹⁷Kansuky, *supra* note 3, at 703.

¹⁹⁸Jordan, *supra* note 1, at 498.

¹⁹⁹Contrera, *supra* note 179, at 953.

²⁰⁰Kansuky, *supra* note 3, at 704.

²⁰¹Dominguez-Urban, *supra* note 2, at 257.

Furthermore, harmonization will hopefully eliminate repetitive testing and requirements such that effective treatment will be able to reach developing nations with less delay.

While improving health in the Third World is in and of itself a benefit of harmonization, it is also beneficial in that it may reduce the spread of disease between nations. When inferior and inefficacious drugs are used by a nation, this could very well have an impact on the entire world. “For instance, antibiotics on developing countries are frequently used in inadequate dosages and for too short a treatment period, resulting in inadequate treatment for the local population and creating drug-resistant strains of bacteria. These bacterial become impossible to treat as they invariably spread throughout the world.”²⁰² The health of nations is also interrelated when one considers the health care implications for citizens of the developed world who travel abroad.²⁰³

Moreover, pharmaceutical harmonization will improve information transfer between countries on public health issues.²⁰⁴

d) Advance International Trade Such that the U.S. will Can Export More

Statistics indicate that U.S. drug companies cannot remain profitable by marketing their products exclusively within in the U.S. Because of the long approval process in the U.S. and the notoriously strict regulatory climate, U.S. pharmaceutical companies have increasingly been performing clinical trials and original product introductions in foreign markets. Because the consumer market in the EU is now larger than the consumer market in the U.S. and because the approval process is generally considered to be faster in the EU, this provides large incentives for U.S. firms to relocate their operations overseas if harmonization fails. Under a

²⁰²Dominguez-Urban, *supra* note2, at 249

²⁰³Dominguez-Urban, *supra* note2, at 249

²⁰⁴Dominguez-Urban, *supra* note2, at 250

harmonized system, the U.S. export position will improve. U.S. drug companies will perform tests at the IND stage, and then will be able to submit a common data package to each of the regulatory participants. Once the foreign regulatory authorities approve the new drugs, the drug companies will be able to export the drugs from the U.S.²⁰⁵

III. THE INTERNATIONAL CONFERENCE ON HARMONISATION

1. Overview

The International Conference on Harmonization (ICH) is a tripartite effort between the United States, the European Union and Japan to harmonize regulatory requirements for the testing, application and approval process of pharmaceutical medications.²⁰⁶ Although the ICH is open to worldwide participation, it focuses on harmonization among the U.S., EU and Japan because they account for 75% of the world's pharmaceutical market and generate 90% of all pharmaceutical research.²⁰⁷

The ICH has two primary goals: 1) to reduce the costs of drugs to consumers by minimizing regulatory problems associated with the need to comply with differing requirements of each 2) increase the safety, efficacy, and quality of pharmaceuticals²⁰⁸

²⁰⁵Jordan, *supra* note 1, at 501.

²⁰⁶Alessandra Cortez, *Introducing the International Conference on Harmonization Guidelines Into the World Trade Organization: A Strategy to Remove Technical Trade Barriers for Pharmaceutical Products*, The International Commercial Diplomacy Project, at http://www.commercialdiplomacy.org/ma_projects/cortez.htm (Spring 2002).

²⁰⁷Kanusky, *supra* note 3, at 667.

²⁰⁸See Michelle D. Miller, *The Informed-Consent Policy of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals For Human Use: Knowledge is the Best Medicine*, 30 CORNELL INT'L L.J. 203, 227 (1997).

2. The Mechanics of the ICH Process

a) Members

The United States, the EU, and Japan each have two active parties in the ICH. One party represents the government regulators and the other represents industry manufacturers. The two parties representing the U.S. in the ICH are the U.S. Food and Drug Administration and Pharmaceutical Research and Manufacturers of America (PhRMA). The EU is represented by the European Commission and by the European Federation of Pharmaceutical Industries' Associations. Finally, the Ministry of Health, Labor and Welfare (MHLW) and Japan Pharmaceutical Manufacturers Association (JPMA) are the representatives for Japan. "In addition to the six participating parties, ICH also includes three observers who act as a liaison between ICH and non-ICH countries and regions. The three observers are the WHO, the European Free Trade Area (EFTA), and Canada."²⁰⁹

b) Structure

The structure of the ICH is comprised of four main groups: the Steering committee, the Expert Working Groups, the Secretariat, and the Coordinators.²¹⁰

The Steering Committee: The steering Committee is composed of two representatives from each of the 6 member parties and one representative from each of the three observing parties. The Steering Committee establishes ICH policies and procedures and chooses topics for harmonization. Additionally, the committee

²⁰⁹ Alessandra Cortez, *Introducing the International Conference on Harmonization Guidelines Into the World Trade Organization: A Strategy to Remove Technical Trade Barriers for Pharmaceutical Products*, The International Commercial Diplomacy Project, at http://www.commercialdiplomacy.org/ma_projects/cortez.htm (Spring 2002).

²¹⁰ *Id.*

supervises the advancement of harmonization initiatives.²¹¹

Expert Working Groups: The Steering Committee appoints an Expert Working Group (EWG) to each of the technical topics selected for harmonization. EWGs represent each of the six members parties, the observers and any other relevant parties (such as the generic drug industry, pharmacopoeias etc.). The groups consist of industry specialists on the topics discussed, and group members are nominated by each of the six parties. EWGs do not have a fixed membership. Rather, they are involved for the timeframe in which their relevant topic is being discussed and/or reviewed.²¹²

The Secretariat: The Secretariat prepares for and documents all of the ICH meetings. Furthermore, they serve as links with any speakers who attend those meetings.²¹³

The Coordinators: The coordinators serve as the primary contact between the Secretariat and the six member parties. Additionally, they make certain that ICH documents are properly distributed.²¹⁴

c) The Process

The ICH process involves five phases. First, the ICH steering committee selects topics for harmonization based on advice from the Expert Working Groups. In this first phase, the Expert Working Groups draft a preliminary statement, which is forwarded to the Steering Committee. The draft includes guidelines, policy statements, recommendations, and points-to-consider. In phase 2, the Steering Committee forwards the draft to the three-member regulatory agencies for formal consultation for a 6-month commitment period. In the third phase, a reporter amends the draft document to account for the comments received from experts

²¹¹ *Id.*

²¹² *Id.*

²¹³ *Id.*

²¹⁴ *Id.*

from the member regulatory bodies. Upon this revision, the EWGs review the amended draft and send it to the Steering Committee for adoption. In phase four, the Steering Committee endorses the final draft and recommends it for adoption by the regulatory bodies of the US, the EU and Japan. Finally, in Phase 5, the three regulatory bodies incorporate the recommendations into their domestic regulations.²¹⁵

2. Implementation of Harmonization In the Three ICH Regions

ICH guidelines, by themselves, have no authority. “The consensus reached through the ICH has neither the force of an international accord nor a treaty; it represents a firm political commitment on the part of the concerned governments.” Each regulatory agency will put into operation its own legislation to make active the guidelines determined at the ICH meetings.²¹⁶ Because there is no system to ensure implementation of the agreements and guidelines, implementation is likely to be a slow process.

a) The United States

The greater part of the FDA’s administrative rules consist of “regulations” and “guidelines.” Regulations signify legal requirements, and therefore take years to formulate. On the other hand, guidelines signify general principles, which the FDA develops in shorter time frames. If a new drug producer adheres to the requirements recommended by the guidelines, the FDA must accept the data. If, however, the drug producer employs a different method, the FDA may reject the data.²¹⁷

Harmonization authority is a part of the FDA’s wide-ranging authority for regulations, approvals, enforce-

²¹⁵Booth, *supra* note 193, at 205.

²¹⁶Kanusky, *supra* note 3, at 695.

²¹⁷Kanusky, *supra* note 3, at 696.

ment and other activities. FDA can undertake the construction of “regulations” that harmonize its regulations with an international standard, so long as the resulting regulation is consistent with the statutes the agency administers. Thus, International harmonization is achieved in the US under the Administrative Procedure Act and Agency Administrative procedure requirements.²¹⁸

However, where a binding requirement is not made, as is the case for most of the ICH guidelines, the process is less rigid.²¹⁹ When Step 2 or step 4 has been reached, the FDA then publishes a notice with the full text of the ICH guidance in the Federal Register for public comment. After considering comments, within the Agency and in collaboration with international partners, FDA publishes a final guidance document in the Federal Register. Notices for Step 2 guidances contain a date for receipt of written comment. Step 4 guidances are available for use in the date they are published in the Federal Register.²²⁰ “In addition to seeking public input through publications of various materials, the FDA provides periodic workshops to discuss the ICH process.”²²¹

b) The European Union

Once ICH guidelines have reached Step 2 or Step 4 of the ICH process, they are submitted to the CPMP for endorsement. The CPMP decides on the length of time that is appropriate for consultation with interested parties (usually 6 months) and the EMEA publishes and distributes the Step 2 guidelines for comments. At step 4, the guidelines are endorsed by the CPMP and a timeframe for implementation is established (also usually 6 months). The guidelines are subsequently published by the European Commission in Volume III

²¹⁸Horton, *supra* note 188, at 710.

²¹⁹Horton, *supra* note 188, at 710.

²²⁰International Federation of Pharmaceutical Manufacturers Associations, *ICH Topics and Guidelines: Efficacy Topics*, International Conference on Harmonisation, at <http://www.ich.org/ich5e.html>.

²²¹Kanusky, *supra* note 3, at 700.

of the Rules Governing Medicinal Products in the European Union.²²²

c) Japan

The Japanese Parliament acts only after the Japanese government agencies, political parties, and business insiders reach a consensus. Usually, an industry committee draws up the preliminary product standard and presents it to the appropriate ministry, although the reverse is also possible. In either situation, the business insiders and the government generally arrive at an agreement before a draft standard is offered for public comment. While a great deal of information regarding regulatory development has been made public in recent years, it is still unclear as to who specifically directs the drafting of the standards. While the Japanese Ministry of Health and Welfare could issue its own rules implementing the ICH principles, the government tends to seek voluntary cooperation from the industry (they tend to choose “guidelines” over “rules”).²²³

Once Step 2 or Step 4 are reached, the ICH texts are translated into Japanese. Subsequently, Pharmaceutical and Medical Safety Bureau (PMSB) Notification for the promulgation or consultation of guidelines written in Japanese is issued with a deadline for comments in the case of consultation drafts, or an implementation date for finalized guidelines.²²⁴

²²²International Federation of Pharmaceutical Manufacturers Associations, *ICH Topics and Guidelines: Efficacy Topics*, International Conference on Harmonisation, at <http://www.ich.org/ich5e.html>.

²²³Kanusky, *supra* note 3, at 701.

²²⁴International Federation of Pharmaceutical Manufacturers Associations, *ICH Topics and Guidelines: Efficacy Topics*, International Conference on Harmonisation, at <http://www.ich.org/ich5e.html>.

IV. Barriers to Achievement of the Goals of the ICH

There remain some considerable barriers that need to be overcome before the harmonization of international pharmaceutical regulations can truly be achieved.

1. Lack of Central Enforcement Authority

The primary barrier to harmonization facing the EMEA and the ICH as a whole is the lack of a central enforcement authority empowered to impose its actions on the other countries.²²⁵ Individual countries' legislatures continue to have ultimate control of implementation. "Without enforcement procedures built into the central system to assure compliance, member countries retain a potential "veto" which in turn jeopardizes the entire system." This is particularly applicable to the U.S. where there is strong ambivalence, both by the legislature and FDA.²²⁶

A lack of enforcement procedures also means that the FDA will go on inspecting foreign manufacturers for compliance with Good Manufacturing Practice and Good Clinical Practice Standards. "Ideally, enforcement would allow a central body to audit practices by all manufacturers and provide independent assurance that ICH adopted standards will be maintained without the need for inspection by each country's own regulatory agency."²²⁷

2. U.S. Ambivalence

²²⁵Kidd, *supra* note 192, at 194.

²²⁶Eakin, *supra* note 186, at 230.

²²⁷Contrera, *supra* note 179, at 946.

While supporting the ICH in theory, the FDA's approach to implementing ICH guidelines "has failed to meet the standards for openness and balanced representation that are necessary for ready acceptance of the ICH standards."²²⁸ "By its own admission, the FDA is pursuing harmonization as a secondary effort while maintaining its primary effort of domestic drug control."²²⁹ Several observers have commented that the U.S.'s idea of harmonization is that its regulations should apply.²³⁰ Two points of concern seem to underlie FDA's ambivalence towards harmonization. One worry is that the FDA, which is normally accustomed to having a great deal of control, will be subjugated to the will of the international community.²³¹ Congress, which ultimately shapes a great deal of FDA policy, "is wary of the potential negative effects of ceding a large measure of control to a foreign entity."²³² The second point underlying U.S. ambivalence is the FDA's fear of compromise of safety and efficacy standards and the FDA's general distrust of foreign data.

The U.S., not at ease with relying on what it may sense is unconfirmed and uncontrolled foreign clinical and manufacturing practices, may perhaps continue to develop Memoranda of Understanding (MOU). MOUs are one of the ways the FDA is attempting to continue oversight of the drugs used by the American populace. MOUs allow the FDA to impress its more stringent standards on foreign countries and also serve to grant authorization for foreign inspections. "Effectively this adds another layer of inspection which potentially slows the overall process through unnecessary redundancy. This result negates the purpose of harmonization."²³³

3. Constitutional Difficulty

One obstacle within the United States confronting the movement towards international harmonization is

²²⁸Booth, *supra* note 193, at 223.

²²⁹Eakin, *supra* note 186, at 228.

²³⁰Eakin, *supra* note 186, at 229.

²³¹Eakin, *supra* note 186, at 236.

²³²Eakin, *supra* note 186, at 237.

²³³Eakin, *supra* note 186, at 228.

the Constitutional difficulty with delegating decision-making authority to a foreign government. The non-delegation doctrine limits the ability of Congress to delegate to administrative agencies the legislative powers vested in it by Article 1 of the Constitution. However, the Supreme Court has rarely ever invalidated on Article 1 grounds acts of Congress which delegated authority to the President or any administrative agency. The Supreme Court has, however, set limits on Congress's ability to delegate authority beyond the bounds of the federal government. Despite the fact that the Supreme Court has never explicitly addressed the issue of delegation to foreign powers, constitutional concerns may apply to an agreement that allowed a foreign regulatory body to bind the FDA to a particular decision. For example, some scholars have argued that Article 43 of the United Nations Charter, which authorizes the UN Security Council to carry out an agreement whereby U.S. forces would serve under foreign command, might violate Congress's Article 1 power to declare war.²³⁴

Case law suggests that the non-delegation doctrine could be overcome as long as the FDA retained the final authority to object particular new drugs.²³⁵

4. Cultural and demographic differences between the Three ICH Regions

a) Differing Attitudes Toward Health and Medicine

There seems to be a general unwillingness of Americans to accept any level of risk regarding pharmaceutical products and, that American attitudes about risk are different from those of other countries.²³⁶ “A study by Sheila Jasanoff revealed variances between citizens of Britain and the United States in their attitudes toward four different types of environmental risk. Jasanoff found that in Britain, scientists and other decision

²³⁴*FDA Reform and the European Medicines Evaluation Agency*, 108 HARV. L. REV. 2009, 2022 (1995).

²³⁵*Id.* at 2023.

²³⁶Kidd, *supra* note 192, at 203.

makers are certain to recognize a risk only when there is persuasive evidence of actual harm... whereas in the United States a risk may also be acknowledged where there is a no direct proof of injury to the public. This cultural diversity of attitude may be compounded in the realm of personal illness—especially terminal disease—where the very notion of ‘risk’ becomes indeterminate and subjective.”²³⁷

Another matter in which attitudes differ in the three regions is in the area of informed consent. This is an obstacle to the development of pharmaceutical standards, particularly in the conduct of clinical trials.²³⁸ The U.S. seems to put a stronger emphasis on informed consent than do Japan and the Europe. Japanese physicians have what Americans view as a ‘paternalistic’ attitude towards informed consent.²³⁹ For example, it is often the case that many patients are not told that they are being placed on an experimental drug. The EU tends to favor medical progress over fully informed consent. They tend to lie somewhere in the middle of the spectrum between the U.S. and Japan.²⁴⁰

Additionally, western manufacturers have refrained from conducting clinical trials in Japan because of their belief that doctors there are frequently unwilling to follow protocols precisely.²⁴¹ “In Japan, when administering a pharmaceutical, the doctor may decide on his own to mix it with dried herbs and roots from the local area to increase its effectiveness.”

Identifiable cultural differences also exist with respect to moral attitudes about certain drug products (e.g., the European ‘abortion’ drug RU-486, or pharmaceuticals developed from the use of fetal tissue research). There also may be differing attitudes toward intensive animal testing.²⁴²

b. Different Physiological Reactions to Drugs

²³⁷ *FDA Reform and the European Medicines Evaluation Agency*, 108 HARV. L. REV. 2009, 2025 (1995).

²³⁸ Miller, *supra* note 208, at 234.

²³⁹ Miller, *supra* note 208, at 220.

²⁴⁰ Miller, *supra* note 208, at 227.

²⁴¹ Kidd, *supra* note 192, 203 n. 160.

²⁴² *FDA Reform and the European Medicines Evaluation Agency*, 108 HARV. L. REV. 2009, 2026 (1995).

An additional barrier to the acceptance of one another's foreign data arises from cultural and demographic differences between the U.S., Europe, and Japan. Certain medical evidence suggests that different racial and ethnic groups have various reactions to pharmaceutical products, such that a drug that is safe and effective in one population groups might be less so in other racial or ethnic groups.²⁴³ If it is the case that differences exist in the way different ethnic groups react to certain drugs, then a research protocol which excludes groups may miss not only the side effects of that particular drug, but may result in a significant positive effect being missed altogether.²⁴⁴

Additionally, there are culturally driven ethnic factors that play a crucial role in the determination of drug equivalence as well as efficacy. These factors include diet, smoking habits, use of alcohol, exposure to pollution, amount of daily sunshine, socioeconomic status, and compliance with prescription drug regimens.²⁴⁵

5. Political barriers

Several authors have noted the close relationship of drug regulatory activities and public policy in any given country. Surrendering this control to a central agency would prove essentially unworkable for many states, which view regulation of drugs as synonymous with national sovereignty. In large part, this has led to the structuring of the ICH without any central enforcement capabilities.²⁴⁶

6. Patent Laws

"There is strong evidence that the vitality of any modern health care system is directly dependant upon a

²⁴³*Id.* at 2025.

²⁴⁴Dominguez-Urban, *supra* note 2, at 264.

²⁴⁵Eakin, *supra* note 186, at 232.

²⁴⁶Eakin, *supra* note 186, at 232.

strong intellectual property regime.” Presently, there is a great dissonance in patent laws around the world. Furthermore, there appears to be little potential for harmonization of patent laws. The chief impediment in the sphere of patents is the United State’s resistance to implementation of a “first to file” system for patent recognition. In contrast to the “first to file system,” which is the de facto international standard, the United States uses the “first to invent” system. While it is acknowledged that a change by the U.S. to the first to file system would necessitate statutory amendment of a system supported by 200 years of case law in the U.S., most U.S. companies doing business internationally are currently working under the “first to file” system with no difficulty.²⁴⁷

7. Mission creep

Another impediment to harmonization of pharmaceutical regulation is “mission creep.” “Mission creep” is an expansion of original objectives to include less focused and less realistic goals. Recognition of a significant need for international collaboration has led some to advocate a sort of “mission creep.” For example, Peter Southerland, former European Community Commissioner for Ireland, has urged the European Federation of Pharmaceutical Industries’ Association to be more aggressive in demanding that non-drug health care technology and treatments be subjected to the same level of regulatory scrutiny as the pharmaceutical industry.²⁴⁸ Standards for such varied things as lawnmowers and electromagnetic radiation, which are beyond the scope of the ICH, are being developed under the general umbrella of the Mutual Recognition Agreement.²⁴⁹ Although consumer safety is the common theme for these products as it is for with drugs, the means and methods of defining and assuring it differ vastly, thus limiting the potential for optimal determination of issues specific to drugs.

²⁴⁷Eakin, *supra* note 186, at 238.

²⁴⁸Kidd, *supra* note 192, at 205.

²⁴⁹Eakin, *supra* note 186, at 239.

8. Global protection of human subjects

There are no international treaties governing experimentation on humans. The trend toward greater acceptance of foreign data and the efforts to harmonize drug regulations can only lead to more research being conducted abroad. To what extent can the countries involved be assured that this research is being conducted ethically? National regulations have very little extra-territorial effect and there are no international treaties governing experimentation on humans.²⁵⁰

9. Harmonizing Upward v. Harmonizing Downward

An additional problem faced by both the EU and the ICH as a whole is that nations with the most rigorous standards are pushing to “harmonize upward” whereas nations with the least stringent standards are pushing to “harmonize downwards.” Both a “race to the top” and a “race to the bottom” would result in an unfavorable outcome. A “race to the bottom” forgoes health and safety standards in favor of freer movement of goods, whereas a “race to the top” would appear to defeat the very objectives of harmonization—reducing the cost of drug development, speeding the process from development to market, and making drugs available to the consumer²⁵¹

V. THE IMPACT OF REGULATORY COOPERATION

1. ICH Accomplishments

²⁵⁰Dominguez-Urban, *note* 2, at 273-276.

²⁵¹Kidd, *supra* note 192, at 195 n.108.

Despite the significant barriers to harmonization, numerous accomplishments have been made under the auspices of the ICH. The principal achievement of the conference is the willingness of all three regulatory agencies to commit publicly to harmonization principles. The FDA's presence at the conference was particularly striking because of their reluctance in the past to accept foreign data.²⁵² The collaborative spirit of the agencies was further evidenced through their agreement to a "de facto moratorium" on the introduction of new clinical testing standards. They viewed the development of potentially inconsistent tests as contrary to harmonization.²⁵³

In addition to this political achievement, there have also been many technical accomplishments. To date, fifty guidelines have been harmonized between the three regions.²⁵⁴ Moreover, they have also developed several products and services to facilitate the harmonization process. These services are designed to help the member parties' manufacturers comply with ICH guidelines and to increase clarity of the guidelines.²⁵⁵ The main products and services developed thus far are the Common Technical Document (CTD), MedDRA, the Electronics Standards for the Transfer of Regulatory Information and Data (ESTRI), and the Global Cooperation Group (GCG).²⁵⁶ As well as discussing these products, this section will highlight some of the important guidelines that have been harmonized.

a) The Common Technical Document

At the fourth ICH conference in July of 1997, the three parties agreed to take on the development of a common

²⁵²Jordan, *supra* note 1, at 495.

²⁵³Jordan, *supra* note 1, at 495.

²⁵⁴Alessandra Cortez, *Introducing the International Conference on Harmonization Guidelines Into the World Trade Organization: A Strategy to Remove Technical Trade Barriers for Pharmaceutical Products*, The International Commercial Diplomacy Project, at http://www.commercialdiplomacy.org/ma_projects/cortez.htm (Spring 2002).

²⁵⁵*Id.*

²⁵⁶*Id.*

technical document (CTD).²⁵⁷ By mid-2001, the CTD application was produced.²⁵⁸ The development of the CTD is considered to be the ICH's most significant achievement thus far. "It is described as a harmoni(z)ed core 'information package' of [clinical, pharmacology/toxicology, and quality] technical data' that can be submitted in the same format and with the same content to obtain marketing authori[z]ation in any of the three ICH regions—the United States, the European Union , and Japan."²⁵⁹ All three regions have implemented a "transition period" from July 2001 to July 2003, during which companies will have the option of submitting marketing authorization applications for any new drugs in either the conventional regional format or the new CTD format. Once the transition period ends in July 2003, the EU and Japan will require that marketing authorization applications be filed in the CTD format and the U.S. will highly recommend that the CTD format be used.

b) MedDRA

In order to make harmonization feasible, the ICH realized that they needed to eliminate regulatory communication barriers. The ICH Steering Committee and EWGs created MedDRA, a medical terminology vocabulary that would allow the EU, Japan, and the U.S. to use one medical language.²⁶⁰ "The multiple dictionaries that were used prior to the creation of MedDRA were often incompatible with one another and lead to communication problems when manufacturers reported their information to multiple regulatory agencies."²⁶¹

²⁵⁷Lofgren & Dreessen, *supra* note 73, at 13.

²⁵⁸Lofgren & Dreessen, *supra* note 73, at 247.

²⁵⁹Lofgren & Dreessen, *supra* note 73, at 245.

²⁶⁰Alessandra Cortez, *Introducing the International Conference on Harmonization Guidelines Into the World Trade Organization: A Strategy to Remove Technical Trade Barriers for Pharmaceutical Products*, The International Commercial Diplomacy Project, at http://www.commercialdiplomacy.org/ma_projects/cortez.htm (Spring 2002).

²⁶¹*Id.*

c) Electronic Standards for the Transfer of Regulatory Information and Data

Because the three founding parties of the ICH are spread across the world, high-speed technology and the Internet are the most efficient means for information exchange and application processing. The ICH Steering Committee delegated an EWG to manage the development of an electronic system for informational exchange between manufacturers and regulatory authorities. The Electronic Standards for the Transfer of Regulatory Information and Data (ESTRI) “covers the evaluation of encryption technologies, physical media (floppy disks and CD-ROMS), network messaging, message formats and electronic document transfers.”²⁶² In 1996, the EWG selected software to handle ICH needs, and since 1997, members of the ICH have been using the software to transfer drug reports.²⁶³

d) The Global Cooperation Group

From the onset of the initiative, members of the ICH have made an effort to uphold a transparent system of practice that would maintain all ICH guidelines and documents open to manufacturers and authorities of all countries. In an attempt to guarantee smooth communication with non-ICH members, the ICH created the Global Cooperation Group (GCG) to serve as an information liaison between ICH member parties and non-ICH member parties. Additionally, the GCG produced a set of principles to be followed when handling requests from non-member parties.²⁶⁴

e) Good Clinical Practice Guidance

²⁶² *Id.*

²⁶³ *Id.*

²⁶⁴ *Id.*

Another considerable accomplishment of the ICH was the adoption of an ICH harmonized Good Clinical Practice (GCP) guidance. A consolidated ICH GCP guidance was released for comment in late 1995 and was subsequently adopted in May 1996.²⁶⁵ This guidance has eliminated many of the considerable differences in clinical trial related regulatory requirement between the three ICH regions. It has also led to the elimination of much of the variability between the EU's Member States.²⁶⁶

f) Stability testing

The members of the ICH have also materialized a set of harmonized procedures for determining the shelf life of new drugs. The procedures, known as “stability testing,” could save money during the development stage of the new drug and during the reexamination stage of the new drug during its lifetime.²⁶⁷

g) Reproductive Toxicology Studies

The testing procedures to determine whether a new drug causes birth defects and/ or affects fertility will also be harmonized.²⁶⁸ So far, the three ICH regions are in agreement that “all female reproduction toxicity studies and the standard battery of genotoxicity studies should be completed before any women who are of childbearing potential and who are not using effective birth control, of whose pregnancy status is unknown, are enrolled in clinical studies.”²⁶⁹

²⁶⁵Russell & Bremer, *supra* note 120, at 59.

²⁶⁶Lofgren & Dreessen, *supra* note 73, at 164.

²⁶⁷Jordan, *supra* note 1, at 493.

²⁶⁸Jordan, *supra* note 1, at 494.

²⁶⁹Russell & Bremer, *supra* note 120, at 23.

h) LD 50 and Other Animal Testing

Additionally, accomplishments have been made in the area of animal testing. A test known as Lethal Dose 50 has been abolished. This test, which was used to determine the lethal dose of new drugs, involved administering increasing dose of the drug to dogs and rodents until half of them died. They resolved to stop requiring twelve-month toxicity studies involving dogs and rodents. Instead the studies will last for 6 months. These arrangements are expected to save the lives of thousands of animals in addition to saving a great deal of money.²⁷⁰

i) Guideline for Safety Pharmacology Studies

In November 2000, an ICH guideline pertaining to safety pharmacology studies reached step 4 of the ICH process. While this guideline has not yet been adopted in the United States and Japan, it has already been adopted in the EU. This guideline provides a general direction concerning which studies are necessary prior to the initiation of a Phase 1 study, which typically include safety pharmacology studies identified in the safety pharmacology core battery.²⁷¹

2. Evaluation of Pharmaceutical Harmonization

While some commentators have been less than optimistic regarding the movement toward global pharmaceutical harmonization, noting that several factors serve as obstacles to the goal, there have been some strong

²⁷⁰Jordan, *supra* note 1, at 494.

²⁷¹This battery of studies has been established to investigate the test article's effects on vital functions specifically the central nervous system, the cardiovascular system, and the respiratory system. Russell & Bremer, *supra* note 120, at 18.

indications of progress resulting from the ICH initiative (see ICH Accomplishments discussed above). It has succeeded in arriving at agreements on topics “such as carcinogenicity testing, statistical principles in clinical trials, viral safety evaluation of biotechnology products, testing of impurities in new drug products, the duration of chronic-toxicity testing in animals, data elements needed for individual case reports of adverse events, and non-clinical safety studies necessary to support the conduct of human clinical trials.”²⁷² Each of these topics had previously been controversial and dealt with differently in each of the three ICH regions.²⁷³ The Development of the CTD in particular is a grand achievement. One of the primary objectives of the ICH “was to remove redundancy and duplication in the development and review process so that a single set of data could be generated to demonstrate the quality, safety, and efficacy of each new medicinal product.”²⁷⁴ This objective is becoming a reality with the development and adoption of the CTD. Moreover, the ICH has had a huge impact on Japan’s drug approval process. Through its willingness to implement ICH developed standards and guidelines affecting both clinical and non-clinical data, Japan has evolved considerably “from an idiosyncratic system unique to Japan”²⁷⁵ to a process that is more consistent with the U.S. and E.U. market.

In fact, the impact that the ICH has had on pharmaceutical harmonization in the three regions has led one commentator to remark that “(t)he days of confusion are over; the ever-changing local regulations are rapidly coming to an end.”²⁷⁶

However, as previously noted, there are considerable barriers to complete pharmaceutical harmonization.

Health Policy is inextricably connected with cultural and societal values and as such has always been the

²⁷²Nancy J. Chew, *ICH Now: Harmony at the End of the Century*, 12 BIOPHARM 24, 27 (1999).

²⁷³*Id.*

²⁷⁴*Id.* at 25.

²⁷⁵Russell & Bremer, *supra* note 120, at 41.

²⁷⁶Chew, *supra* note 272, at 27.

focus of intense politicization by regional and national governments.²⁷⁷ With this in mind, it seems likely that the individual countries will maintain ultimate veto power with regard to approval of a single drug or drug product.²⁷⁸

CONCLUSION

Harmonization of the technical regulations for drug approval in the United States, Europe, and Japan is a worthy goal. The United States, the EU, and Japan each regulate pharmaceuticals for the welfare of their citizens. However, each country advocates its own system of laws controlling production and testing of pharmaceuticals. Differences in the national regulations generate costs for drug manufacturers and ultimately for consumers. Moreover, they lead to delays in the worldwide introduction of new drugs. The International Conference on Harmonization has been a significant effort in eliminating the problems of unnecessary costs and delays in drug approval.

With the successful completion of the first phase of activity behind them, the ICH will move into the second phase with the continuing commitment to increased international harmonization. Due to the success of the initiative thus far, more interest has been generated in the initiative from regulatory and industry bodies outside of the U.S., the EU, and Japan.²⁷⁹ It will therefore be increasingly important to make certain that the goals and outcomes of the ICH are comprehensible and more widely disseminated.²⁸⁰

²⁷⁷Eakin, *supra* note 186, at 243.

²⁷⁸Eakin, *supra* note 186, at 245.

²⁷⁹International Federation of Pharmaceutical Manufacturers Associations, *ICH Past and Future*, International Conference on Harmonisation, at <http://www.ich.org/ich8.html>.

²⁸⁰*Id.*