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The International Conference on Harmonization of Pharmaceutical Regulations, the European Medicines Evaluation Agency, and the FDA: Who’s Zooming Who?

DAN KIDD*

INTRODUCTION

In the early 1990s the pharmaceutical industry underwent a worldwide period of stagnation due to cost-containment pressures from governments and insurance companies. Pressure from the government came in the form of many small and some not-so-small regulatory reforms. Variations and inconsistencies in the regulatory schemes of the major drug markets resulted in slower drug development, higher prices, and unfair competition. For at least the past fifteen years, the dominant force behind the regulatory reforms in the United States has been the idea of globalization. Many people in the government, the pharmaceutical industry, and the public firmly believe that international harmonization of regulatory standards would remedy the situation.

The industry probably began thinking and acting globally before governments did. For many years, large multinational corporations have been the rule rather than the exception in the drug business. The governments of the United States, Japan, and Europe could not effectively act globally until

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4. See generally James Gomez, O.C. Medical Device Companies Await Marketing Breakthrough in Europe Sales, L.A. TIMES, Aug. 9, 1992, at 1D (noting that drug companies are developing strategies to take advantage of EC regulatory standardization).

5. The United States, Europe, and Japan account for more than 80% of the world’s pharmaceutical

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1990 when the European Community (EC) Council approved the necessary steps for drafting of the Maastricht Treaty, finalizing the creation of the European Union (EU). However, around that time, those governments did act, in partnership with the industry, by forming the International Conference on Harmonization of Technical Requirements of Pharmaceuticals for Human Use (ICH).

There are several major forces at work behind international harmonization as envisioned by the ICH: a borderless Europe under the EU, a drug industry that is on the verge of a gold boom period, and an FDA which is under continual pressure both from inside and outside the agency to be ever more efficient. ICH holds out the hope that pharmaceuticals can be researched, developed, and approved under one set of scientific standards that are rigorous enough to satisfy the most thorough FDA investigator yet lenient enough to allow the free flow of drugs throughout the industrialized world. Whether the ICH can strike this delicate balance, with the various competing interests pushing and pulling in a myriad of directions, is the subject of this Note.

Some form of international harmonization of the pharmaceutical industry is inevitable, but whether it will be positive or negative is far from certain. More importantly, how harmonization will be achieved is not at all clear. Will the collaborative process of the ICH be continued and expanded? Will the EU drug regulatory systems become the model for global harmony? Will the FDA establish itself as the premier drug regulatory agency, forcing the rest of the

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6. The EU was originally called the European Economic Community (EEC), then the European Community. George A. Bermann et al., Cases and Materials on European Community Law, 16, 18, 22, 23 (1993). The Maastricht Treaty implemented several directives designed to create a truly borderless society among the Member States, including giving the EU binding authority on health care issues. David Vogel, Regulatory Interdependence in a Global Economy: The Globalization of Pharmaceutical Regulation (Aug. 1995) (unpublished manuscript, presented at the Annual Meeting of the American Political Science Association) (on file with the Ind. J. Global Legal Stud.).


9. The push for efficiency is a double-edged sword for the FDA. In the long term, harmonization holds out the promise of improved efficiency, but a fiscally conservative Congress may not be willing to support harmonization activities which do not have at least some immediate, short-term benefits.
world to follow it? In this Note, I attempt to address these possibilities and explore the problems associated with each.10

Section I of this paper will review the short history of the ICH to date. Section II will discuss the two-tier approval process of the EU. Section III will examine at the direction of the FDA’s approval procedure and enforcement division. Finally, Section IV will address some of the other major barriers to international harmonization.

I. HISTORY OF THE ICH

The idea for the International Conference on Harmonization originated in a joint mission between Japan and the EU in 1988. The Conference was comprised of representatives from the EU’s Committee for Proprietary Medicinal Products (CPMP) and the European Federation of Pharmaceutical Industries’ Associations (EFPIA).11 The mission’s goal was to resolve differences between the safety and efficacy requirements of the various countries.12 Meanwhile, another EU agency was meeting with FDA and Japanese officials in Japan.13 In 1989, a conference between the regulatory officials and the International Federation of Pharmaceutical Manufacturers Associations (IFPMA) led to the creation of the ICH process.14

The ICH has two major goals. First, the countries and companies involved want to harmonize the scientific requirements of the pharmaceutical regulatory schemes in the United States, the European Union, and Japan. ICH is not intended to replace the drug approval procedures of the participants.15 Instead, it is hoped that if the regulatory agencies all require the same data, differences in the processes of approval will be of less significance than is currently the case.16 Underlying the goal of harmonization, the second and ultimate goal of

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10. An evaluation of Japan’s possible influences on the harmonization processes is beyond the scope of this Note.
12. Id.
13. Id.
14. Id. at 939-40.
15. ICH does not promulgate, and is in fact powerless to promulgate, any binding regulations. ICH issues harmonized guidelines which become binding only if enacted into law by each of the individual nations by their normal legislative processes. Id. at 954-55.
16. Although there will still be national differences in how the data is interpreted, harmonizing the procedure of approval is seen as an important first step toward globalization.
ICH is to speed up the time from development to marketing of new drugs. The first goal may be achievable, but there is no guarantee that it will lead to achievement of the second. If it does, it will be the first time that major regulatory reform has decreased the time from development to market for new drugs. The worst possible scenario would be that ICH would simply add another layer of bureaucratic red tape to an already over-regulated industry.

The United States, represented by the FDA, similar agencies of the European Union and Japan, and industry representatives came together in 1991 for the First ICH (ICH1) in Brussels, Belgium. The ICH1 participants agreed to drop a controversial animal-based test, LD-50. They also agreed to work toward harmonizing stability-testing guidelines and generally clarified several cross-national misconceptions about pharmaceutical regulations and scientific definitions. Most importantly, they established a process of negotiated rulemaking whereby harmonized guidelines could be developed. Seen as more of a momentous political summit than a scientific conference, ICH1 set the stage to launch the pharmaceutical industry into a worldwide political player, influencing health care and economic decisions at the highest levels of government.


18. Over 1000 participants attended ICH1. Vogel, supra note 6, at 22.

19. Global Harmonisation, supra note 7. The Lethal-Dose 50 test was conducted by administering differing levels of doses to laboratory animals to determine the dose at which 50% of the animals died. Vogel, supra note 6, at 23 n.75.

20. Global Harmonisation, supra note 7. Stability testing is the measurement of a drug’s shelf life under a variety of storage conditions (humidity, temperature, etc.).

21. Vogel, supra note 6, at 23. For example, before ICH, the EU, Japan, and the United States lacked a common definition of "room temperature." Now, that term, as well as other laboratory control conditions, are precisely defined. Id.

22. Contrera, supra note 11, at 940. Rulemaking proceeds under the ICH as follows: (1) the Steering Committee (SC) appoints expert working groups (EWG); (2) the EWG prioritizes the problems posed by inconsistent regulation and the likelihood of obtaining a consensus toward harmonization; (3) the EWG makes recommendations to the SC, which forwards the draft to the respective regulatory agencies in each of the three countries for formal consultation; (4) the draft guidelines are modified by the regulatory agencies, then returned to the EWG for their final approval; (5) the EWG then sends the final draft back to the SC; (6) the SC either approves or makes changes to the draft text, then submits the harmonized guideline to the respective agencies for adoption into their national laws according to national or regional procedures. Id. at 940 n.57.

In October 1992, ICH2 took place in Orlando, Florida, with over 1600 scientists and health authorities in attendance. The conference achieved significant advances toward harmonization in the following areas: reducing the need for animal-based experiments detecting toxicity to reproductive systems; guidelines for drug studies in the elderly; and establishing definitions and standards for clinical safety data management. Agreement was also reached for issuing draft guidelines covering many facets of Good Clinical Practices (GCPs). The draft included guidelines for investigators, definitions and terminology for analytical method validation, and guidelines on the number of patients necessary to assess clinical safety of certain long-term drugs.

In November, 1995, some 2400 delegates representing pharmaceutical companies and forty governments took part in ICH3, which was held in Japan. ICH3 focused on further harmonizing international guidelines for clinical testing of new drugs. Major changes in that area are expected in Japan. Currently, Japanese regulations do not require the written, informed consent from patients participating in clinical trials. The new agreement places greater onus on the manufacturers during the proposal stage of clinical testing to ensure compliance with the new rules.

Standardizing the requirements of the pre-clinical stage of drug development was notable but the real work is still ahead. A potential drug spends a relatively short time in the pre-clinical stage, hence the majority of regulations apply to the clinical stages and beyond. If ICH3 succeeds in harmonizing the clinical trial stage requirements, several areas of

25. Id.
26. Id.
31. Once a potential drug is identified in the laboratory as possibly effective against a particular disease or illness and a reliable method of manufacturing has been developed, the drug moves into the "clinical" stage.
32. A harmonized guideline for GCPs was adopted by the ICH and is in the process of approval in the United States, Japan, and the European Union. ICH Steering Committee Expert Groups Meet, MARKETLETTER, May 13, 1996, available in 1996 WL 9648709. At ICH3 it was also agreed to develop a harmonized dictionary of medical terminology to be used by the industry and regulatory agencies worldwide. Int'l Organization to be Created to Maintain "Regulatory Terminology", PHARMA JAPAN, Apr.
pharmaceutical development and marketing come to mind as potential candidates for harmonization. Such areas include drug labeling and advertising, post-approval monitoring of adverse side effects, use of Good Manufacturing Practices (GMPs) and Good Laboratory Practices (GLPs). Originally, ICH was envisioned to be a six-year process, but ICH4 is already being planned for 1997 in Belgium.33

II. REGULATORY HARMONIZATION WITHIN THE EUROPEAN UNION

A. The EU Approach to New Drug Approvals

With the EU now representing eighteen countries and more than 370 million people,34 it is the world’s largest integrated pharmaceutical market. In 1993, it accounted for more than seventy billion dollars of the world market.35 The EU’s pharmaceutical industry ranks fourth of all industries when it comes to being hindered by inconsistent technical regulations.36 The countries of the EU anticipated the importance of a borderless pharmaceutical market long before the world as a whole.37 The road to a borderless pharmaceutical society in the EU, however, has been plagued by numerous setbacks.38 Directive 65/65 EEC39 laid the groundwork in 1965 to establish a borderless drug market. However, the centralized European agency for drug approvals, the European Medicines Evaluation Agency (EMEA), did not become a reality until thirty years later.40 The EU Commission has found it very difficult to legislate EU-wide pharmaceutical regulations because Member States

35. Europe’s Pharmaceutical Industry in 1993, supra note 5.
37. See Vogel, supra note 6, at 8.
tenaciously cling to control over health care and the drug industry as one of the

The EU efforts to harmonize can be studied as a prototype for the larger, international approach being advocated by ICH. The direction Europe takes during the next four or five years may be the precursor of where ICH is headed. This section will discuss the two current drug approval systems in the EU--how they work, how they evolved, how they may continue to evolve, and how they may be used to predict the future of international harmonization on a larger scale.

1. The Multistate Procedure 1975 - 1995

In 1975, the EU created the Committee for Proprietary Medicinal Products (CPMP) and a multistate procedure, sometimes called mutual recognition, for approvals.\footnote{Orzack et. al., supra note 38, at 855-56.} Prior to 1975, manufacturers who wished to market their products in different Member States had to apply separately to each individual State, and then the States either approved or rejected the application with no regard to the decision of their neighbors.\footnote{Individual approvals are costly for the industry because they often result in making the same product subject to different control testing during the manufacturing process. Since most manufacturers do not know, during the critical manufacturing process, where a particular lot will ultimately be marketed, they are forced to either “overtest” the product or manufacture specific lots for each market.} The CPMP includes representatives from all Member States and also from the European Commission.\footnote{Orzack et al., supra note 38, at 855.} The CPMP’s mandate was to replace the drug regulatory systems of the EC’s twelve existing Member States EC with a single supervisory agency.\footnote{Id.} Under the mutual recognition system, a drug manufacturer could apply for approval in one Member State, and once approval was granted there, the manufacturer could seek approval in as many as five other member States at the same time.\footnote{Id. Manufacturers were not required to use the new system. They could still seek individual approvals from each country in which they wished to market their products. Id.} The regulatory bodies in those States could learn from the CPMP that at least one other Member State had granted approval for the drug.\footnote{Id.} In theory, the
additional States were required to consider the initial approval when conducting their own reviews; in practice, however, they retained broad authority to raise an objection and could thus decide not to admit a certain product even if it was recommended by the CPMP.\textsuperscript{48}

Instead of opening the national markets by speeding the approval process, the multistate procedure caused numerous delays as the individual countries routinely raised objections to mutual recognition.\textsuperscript{49} In 1988, the CPMP noted that "there have been objections with regard to every case dealt with under the Multi-State [sic] procedure . . . ."\textsuperscript{50} The CPMP Chairman concluded that "[o]n the whole the Member States do not yet accept each other's assessments."\textsuperscript{51} Although the new system resulted in Member States participating in the CPMP process, final approval has "clearly remained with national bodies."\textsuperscript{52}


Beginning in 1995, a new multistate procedure, sometimes called "mutual recognition," went into effect to strengthen the authority of the CPMP decision.\textsuperscript{53} Under the new system, a company applies to one Member State first, which makes a decision and issues an assessment report.\textsuperscript{54} The company can then apply to additional States and the assessment report is forwarded to them and to the CPMP.\textsuperscript{55} The additional countries have ninety days to decide whether to accept or deny the initial approval.\textsuperscript{56} The directive requires Member States to recognize the original approval unless "there are grounds for supposing that . . . the medicinal product concerned may present a risk to public health."\textsuperscript{57} The directive also allows Member States to approve a product

\textsuperscript{48} Id.
\textsuperscript{49} Id.
\textsuperscript{50} Id. (quoting C.A. Teijgler, \textit{The Role of CPMP in the EEC, in} \textit{INTERNATIONAL MEDICINES REGULATIONS: A FORWARD LOOK TO 1992} (S.R. Walker and J.P. Griffin, eds., 1989).
\textsuperscript{51} Id.
\textsuperscript{52} Id. at 858.
\textsuperscript{54} Kingham et al., supra note 53, at 310.
\textsuperscript{55} Id.
\textsuperscript{56} Id.
\textsuperscript{57} Directive 93/39, supra note 53, art. 3.1, at 26. Unlike the previous system, the new directive does not permit a Member State to refuse recognition if approval would be contrary to their patent or "exclusivity" laws. This may create a conflict with other EU directives governing periods of exclusivity. The European Court of Justice may have to resolve this difficult dilemma. Kingham et al., supra note 53,
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pursuant to special conditions but must be imposed only for "objective and verifiable reasons." Disputes are referred to the CPMP which issues an opinion on the matter. Under the new system, the opinion is made binding by going through the same tedious Commission and Council procedure as for concertation, described in the next section.

Some indication of the general nervousness about the new multistate system was the surge in last-minute filings under the old multistate procedure. Multistate filings under the old system doubled in the final three months of 1994, bringing the total for the year to sixty-four (previously the average had been approximately fifty per year).

In addition to the new multistate system, drug firms may continue to pursue individual country approvals until 1998. However, as of January 1, 1998, "any Member State that receives an application for a drug that is already approved by another EC country is required to automatically recognize that approval." This should make mutual recognition mandatory, but the Member States will still have the option to refer the matter to the CPMP for arbitration. If the old system is any indication, referrals will become the norm and approval times will most likely increase, at least in the short term.


In 1987, the concertation procedure was introduced through Directive 87/22 EEC. The concertation system applies to the small but important class of products developed from biotechnology or "high technology." Limiting

at 319.

59. Id. art. 13, at 24-28.
62. Id.
63. Kingham et al., supra note 53, at 311-12.
64. Id. at 312.
65. Id. at 315.
67. Orzack et al., supra note 38, at 856. "Biotechnology products" refers to those derived from DNA technology such as Eli Lilly's insulin drug, Humulin, genetic coding of biologically active proteins, and monoclonal antibodies. High technology medicines include compounds based on radioisotopes, products administered by technologically advanced delivery systems, and products resulting from major technical or scientific breakthroughs. Id. at 856-57.
the products covered by this system was thought necessary in order to allow a gradual transfer of power from the Member States to the EC. While companies making such products from biotechnology were required to use this procedure, high-tech products were permitted, but not required, to use it.\textsuperscript{69} Under this procedure, a manufacturer submitted an application to the CPMP and one Member State at the same time.\textsuperscript{70} That Member State’s regulatory agency acted as a rapporteur to the CPMP.\textsuperscript{71} The rapporteur had a stated maximum of 210 days after receipt of a valid application to issue its report to the CPMP, but that did not include time spent by the applicant providing additional information or explanations.\textsuperscript{72} The CPMP was also required to issue its own advisory report within 180 days of the original submission, which the rapporteur could consider when writing its opinion.\textsuperscript{73}

Once the rapporteur’s evaluation was received, the manufacturer could then submit the application to other Member States.\textsuperscript{74} The CPMP and the rapporteur acted as communication facilitators between the applicant and the other Member States.\textsuperscript{75} The CPMP oversaw and commented upon all applicant responses.\textsuperscript{76} After all requests for information had been satisfied, the CPMP issued an opinion recommending approval or disapproval.\textsuperscript{77} Member States then had thirty days to decide whether to follow the CPMP recommendation.\textsuperscript{78}

4. The Concertation Procedure After 1995

EU Regulation 2309/93\textsuperscript{79} established the EMEA to coordinate the evaluation of scientific data associated with the approval, manufacturing, and inspection of medicines in the EU.\textsuperscript{80} The EMEA is designed to be an advisory

\begin{itemize}
\item \textsuperscript{68} Evelyne Friedel & Michael Freundlich, \textit{European Community Harmonization of the Licensing and Manufacturing of Medicinal Products}, 49 FOOD & DRUG L.J. 141, 163 (1994).
\item \textsuperscript{69} Orzack et al., \textit{supra} note 38, at 857.
\item \textsuperscript{70} Id.
\item \textsuperscript{71} Id.
\item \textsuperscript{72} Friedel & Freundlich, \textit{supra} note 68, at 158 n.90.
\item \textsuperscript{73} Id. at 158.
\item \textsuperscript{74} Orzack et al., \textit{supra} note 38, at 857.
\item \textsuperscript{75} Id.
\item \textsuperscript{76} Id.
\item \textsuperscript{77} Id. at 158.
\item \textsuperscript{78} Id. at 306.
\item \textsuperscript{79} The recommendation was not legally binding. Friedel & Freundlich, \textit{supra} note 68, at 158.
\item \textsuperscript{80} Friedel & Freundlich, \textit{supra} note 68, at 159-60.
\end{itemize}
agency only, providing supervision to the CPMP and the national authorities. The regulation also repealed Directive 87/22 EEC. The concertation procedure remains mandatory for biotechnology products and optional for other high-technology products, but the new procedure should result in one marketing approval that will be valid throughout the EU.

Under the new system, applications are submitted directly to the EMEA, which refers the matter to the CPMP for review. Within 210 days the CPMP must issue an opinion determined by a simple majority vote. If the CPMP votes for approval, the opinion is forwarded to the European Commission, all Member States, and the applicant. The Commission prepares a draft decision and forwards it to all concerned. The Commission then consults with the Standing Committee on Medicinal Products for Human Use (composed of representatives from all Member States, voting by a weighted majority). If the Standing Committee affirms the draft decision, it becomes final. If they reject the Commission's decision, the issue must be decided by the European Council. The Council can support the Standing Committee by voting to reject the draft decision; however, if they fail to do so within ninety days, the decision becomes final.

This complex and time-consuming process is necessary to render a decision which is binding on all Member States and thus avoid the pitfalls of the old multistate procedure. Unlike the FDA, which has congressional authority to enact binding national regulations, the EMEA and CPMP have no such power. Those agencies thus centralize the approval process for the most innovative types of drugs, but unfortunately, they still cannot bind the national authorities. Nonetheless, it is hoped that the new procedure will be less

81. Id. at 160.
82. Id. at 159.
83. Id. at 163.
84. Id.
85. Kingham et al., supra note 53, at 306.
86. Id. at 306-07.
87. Id.
88. Id.
89. Id. at 307.
90. Id.
91. Id.
92. Id.
93. Orzack et al., supra note 38, at 857-58. Due to the CPMP's dismal record in facilitating mutual approvals under the previous system, there was considerable criticism of sanctioning the new system. Id.
delay-prone than the old concertation system and less costly for small drug firms, inducing them to expand their markets.\textsuperscript{94}

\textbf{B. Problems with EU Harmonization}

Continuing evolution of the EU systems for drug approval is evidence that the EU has not found a completely satisfactory process. This evolution also indicates that the national governments, the Commission, and the industry recognize the need for constant re-evaluation and optimization. Although both multistate and concertation procedures require Commission action to resolve disputes and create binding arbitration opinions, it is expected that if CPMP action is routinely approved by the Commission, the number of cases requiring their intervention will dramatically decrease.\textsuperscript{95} Thus, the EU is headed toward a centralized authority for all drug approvals. Innovative medicines will be the first products to be approved or disapproved under an EU-wide system, but once the system is optimized, other drugs will surely follow. Despite these advances, some of the problems in the system remain.

Several of the problems that the EU has experienced (or is experiencing) also have wider implications for harmonization among the EU, Japan, and the United States. Perhaps the biggest issue facing the EMEA and the ICH is how much centralized authority is necessary and how much is possible. The European Commission issued a draft Notice to Applicants in December 1994, which reiterated the central tenet of the mutual recognition system; “authorisation . . . in one Member State ought in principle to be recognised by the competent authorities of the other Member States” (unless there is an objection based on serious concern for public safety).\textsuperscript{96} However, the Commission and the executive director of the EMEA have alarmed some members of the industry by claiming that the national authorities will remain the “pillars” of the new system.\textsuperscript{97}

In some countries, objections to new drug applications are the norm, yet the EMEA is powerless to prevent such objections because “there is no legal mandate” behind mutual recognition.\textsuperscript{98} The EMEA and the Commission's procedures are “designed to facilitate, not impose, harmonisation,” and the

\textsuperscript{94} Friedel & Freundlich, supra note 68, at 164.
\textsuperscript{95} Kingham et al., supra note 53, at 315.
\textsuperscript{96} No Rubber Stamp, supra note 61.
\textsuperscript{97} Id.
\textsuperscript{98} Id.
Commission seems content to rely on the hollow axiom that "science doesn't
recognize national boundaries."\(^{99}\) The role of the EMEA, according to its
executive director, is "mainly to provide the infrastructure for cooperation."\(^{100}\)
This role sounds strikingly similar to the one advocated for the ICH. The EU
may eventually be forced to delegate decisionmaking powers to the EMEA in
order to achieve a workable, harmonized process,\(^ {101}\) but it seems highly
implausible that the ICH will ever be granted such power.

Another problem in the EU is the apparent assumption that the national
regulatory agencies are more alike than they are different.\(^ {102}\) Differences in
social and cultural attitudes toward healthcare risks, individual rights, and
governmental responsibilities also cannot be ignored.\(^ {103}\) There is perhaps more
cultural harmony between the EU countries than among the ICH countries.
Differing levels of political power can also affect harmonization efforts.
France, Germany, and the United Kingdom pressured the EU to ban
pharmaceutical parallel imports from Spain and Portugal in 1985, and the ban
was extended in the fall of 1995.\(^ {104}\) Northern European drug manufacturers
claim that cheap imports from the two countries would cost domestic
manufacturers up to two billion dollars per year.\(^ {105}\) The fact that the EU has
not been entirely successful in resolving these differences does not bode well
for the ICH.

Another problem faced by the EU and the ICH alike is that nations which
have the most rigorous standards are pushing to "harmonize upward" versus
the least stringent nations pushing to "harmonize downward."\(^ {106}\) A "race to the
bottom" sacrifices health and safety standards in favor of freer movement of
goods.\(^ {107}\) A "race to the top" would result in the opposite, but equally
undesirable outcome.\(^ {108}\) Other problems faced by the EU and the ICH are

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99. Id. This statement ignores the reality of the situation; if science didn't recognize national borders,
there would be no need for harmonization.

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101. This process could only be accomplished from the bottom up—the individual countries would
have to authorize the EU Council to delegate authority to the EMEA.

102. Orzack et al., *supra* note 38, at 859.


in 1995 WL 2154506. Spain and Portugal did not have patent legislation to protect drug makers until 1992.

105. Id.

106. Orzack et al., *supra* note 38, at 861.

107. Id.

108. Moving in the direction of the highest standards would appear to defeat the very objectives of
national differences in the following areas: enforcement capabilities; patent protection; health care systems and insurance coverage; and forms and levels of governmental subsidies, both to the consumer and the manufacturer. Some measure of uniformity in these peripheral areas, while not absolutely essential to harmonization of the scientific aspects of pharmaceuticals, would nonetheless make harmonization more effective. Whether the EU can find a successful way to deal with these problems without sacrificing harmonization objectives will provide some indication of whether global harmonization is truly possible.

III. THE FDA'S IMPACT ON INTERNATIONAL HARMONIZATION

Just as the pharmaceutical world began working toward international harmonization, two changes affecting the FDA occurred that might seriously impact harmonization efforts. First, Congress allowed the agency to expand its enforcement division, and second, Congress passed the Prescription Drug User Fee Act of 1992. Although neither of these developments were undertaken with the intent to undermine the ICH, they may unfortunately have that effect because they demonstrate that the FDA and the ICH are moving in different directions.

A. The Prescription Drug User Fee Act of 1992

The United States has a very conservative approach to drug regulation, with perhaps the most rigorous and demanding approval procedures in the world. Under current FDA rules, a new drug must satisfy stringent safety and efficacy requirements before receiving approval for marketing. The

109. Contrera, supra note 11, at 955; Kingham et al., supra note 53, at 317-19; Orzack et al., supra note 38, at 865.
111. Dillman, supra note 17, at 925.
112. Note, FDA Reform, supra note 17, at 202. A new drug must undergo four stages of investigation under the auspices of the FDA before marketing approval is granted. Julie C. Relihan, Expediting FDA Approval of AIDS Drugs: An International Approach, 13 B.U. INT'L J.L. 229, 235 (1995). First, a drug must satisfy several pre-clinical hurdles which are designed to evaluate the drug's toxicity to humans. After the drug is found to be reasonably safe for humans, the manufacturer files a Notice for an Investigational New Drug (IND) with the FDA. This document must contain, among other things, all preclinical data information, detailed descriptions of the drug's composition, manufacturing and quality
FDA and its supporters believe that the myriad of regulations are absolutely necessary to prevent dangerous drugs from reaching the U.S. market. When one considers that virtually all major legislation regarding pharmaceuticals has been the direct result of public health tragedies, it is hard to argue for dismantling the present structure.

In recent years, however, many people have argued for dismantling the system. The FDA is frequently criticized for an alleged "drug lag" between the United States and European countries. It is estimated that this drug lag has caused thousands of needless deaths due to the unavailability of lifesaving drugs. The FDA responded in the early 1990s by loosening restrictions on the availability of some experimental drugs and accelerating the approval process for promising new drugs through a variety of means, including the User Fee Act. The passage of the User Fee Act was "the biggest change at the FDA in thirty years." The Act permits the FDA to charge a fee for reviewing a company's drug application; the monies generated will allow the

control methods, an outline of proposed phases for further investigation, and an agreement by the manufacturer to report all serious side effects. Clinical trials on humans may begin 30 days after the FDA receives the IND. Dillman, supra note 17, at 928.

Human clinical trials occur in three or four phases. Phase I involves a very small group of healthy test subjects and focuses on the drug's absorption, rate of metabolism, and elimination. Any toxic effects undetected during preclinical studies would hopefully be discovered during this phase. Phase II testing involves a small population of symptomatic patients and allows the manufacturer the first opportunity to evaluate the drug's efficacy in human subjects. Phase III is the costliest stage in the development of a new drug. It may involve thousands of patients in dozens of clinical sites around the world. Id. at 928-29.

At the end of Phase III testing, which may last several years, the manufacturer may file a New Drug Application (NDA). The NDA contains all manufacturing and testing data concerning the final drug composition. The NDA may consist of hundreds of binders containing tens of thousands of pages of data. The FDA reviews all of this data and then decides to approve or disapprove the drug. Id. at 930.

113. Note, FDA Reform, supra note 17, at 204.
114. Id. at 2012; C. Frederick Beckner, III, Note, The FDA's War On Drugs, 82 GEO. L.J. 529, 529-30 (1993); Contrera, supra note 11, at 932-35.
115. Beckner, supra note 114, at 529; Dillman, supra note 17, at 925; Linda Domey, Comment, Culpable Conduct with Impunity: The Blood Industry and the FDA's Responsibility for the Spread of AIDS Through Blood Products, 3 J. PHARMACY & L. 129, 130-31 (1994); Kibbe, supra note 3; See Relihan, supra note 112.
116. Dillman, supra note 17, at 934; Note, FDA Reform, supra note 17, at 2014; Randall Mikkelsen, FDA Red Tape Pushes Testing Overseas, Drug Maker Says; Congressional Reforms to Speed up Approvals are Needed, Hoffman-LaRoche President Says, THE ORANGE COUNTY REGISTER (Cal.), Aug. 18, 1995, available in 1995 WL 5866076.
117. Note, FDA Reform, supra note 17, at 2014.
118. Id. at 2015.
119. Relihan, supra note 112, at 244.
agency to expand its review staff by fifty percent.\textsuperscript{120} The industry generally welcomed the Act’s passage.\textsuperscript{121}

The agency claims these measures have decreased the approval times for new drugs from 26.7 months in 1993 to just 19 months in 1994. In late 1995, the agency announced that the supposed drug lag had been conquered.\textsuperscript{122} Critics of the FDA maintain, however, that approval times have decreased because the agency is asking for substantially more clinical data up front, before the FDA review “clock” starts running.\textsuperscript{123} The critics also claim that the User Fee Act, while helping important new drugs gain faster approval, has caused other non-lifesaving medicines to pay the cost with increased approval times.\textsuperscript{124}

The debate over approval times, however, seems to focus on the wrong question; the real issue is whether all those regulations are in fact necessary. ICH is attempting to answer this question. If the User Fee Act accomplishes what it is supposed to accomplish—speeding the approval process—that may just institutionalize the overkill. If ICH guidelines end up at odds with FDA regulations, the FDA may derail ICH goals by digging in its heels as the next section demonstrates.

B. FDA Enforcement Initiatives

The FDA’s approval requirements are especially rigorous because the FDA has perhaps the world’s foremost enforcement division. FDA Commissioner, David Kessler, has made enforcement the agency’s top priority.\textsuperscript{125} A fundamental tenet of the FDA’s enforcement philosophy is that most firms and most people have a genuine desire to comply with the regulations.\textsuperscript{126} Nonetheless, the FDA has a wide assortment of enforcement

\begin{enumerate}
\item \textsuperscript{120} Id.
\item \textsuperscript{121} Conrera, supra note 11, at 959-60.
\item \textsuperscript{122} Note, FDA Reform, supra note 17, at 2015; Lauran Neergaard, FDA Report Aims to Deflect Criticism that It’s Slow in Approving New Drugs, THE INDIANAPOLIS STAR, Dec. 13, 1995, at A16.
\item \textsuperscript{123} Note, FDA Reform, supra, note 17 at 2015. The FDA may not necessarily be asking for more information, but instead may be only more clearly defining what information is necessary for an acceptable submission.
\item \textsuperscript{124} Id.
\item \textsuperscript{125} Arvin P. Shroff, FDA Enforcement Initiatives in the United States and Abroad, 49 FOOD & DRUG L.J. 575, 575 (1994). The FDA has approximately 3900 employees engaged in inspection and enforcement activities. Alan L. Hoeting, The FDA’s Enforcement Program, 47 FOOD & DRUG L.J. 405, 406 (1992).
\item \textsuperscript{126} Marie A. Urban, The FDA’s Policy on Seizures, Injunctions, Civil Fines, and Recalls, 47 FOOD
tools available to ensure compliance. These tools include administrative, civil, and criminal measures. In recent years, the FDA has raised the civil penalties for violations, and it increasingly seeks criminal convictions by joining forces with other federal agencies, like the Department of Justice, to investigate and prosecute violators.

The FDA has extremely broad authority over imported materials; however, by increasing its control over the domestic market the FDA continues to expand its influence over foreign drug manufacturers and suppliers. By expanding the regulations vertically to cover production, storage, testing, transportation, and labeling of every raw material or ingredient used in the manufacturing of a domestic pharmaceutical, the power of the FDA reaches well beyond U.S. borders.

This "vertical enforcement" can be seen in the FDA's efforts to regulate the bulk pharmaceutical industry. Between seventy and eighty percent of bulk pharmaceutical chemicals (BPCs) used for over-the-counter drugs are imported into the United States, yet the FDA "really doesn't have any good data" regarding compliance with regulations covering GMPs because the FDA inspects few foreign bulk sites. The agency has increased its enforcement and inspection efforts of foreign BPC suppliers, but often the damage is done before the FDA learns about it.

FDA regulation of foreign BPC suppliers could theoretically harm other ICH countries that depend on those suppliers for raw materials because it gives the FDA power to pull strings behind the scenes.

When a foreign manufacturer applies for approval to market a finished product in the United States, the FDA conducts a full inspection of its manufacturing and testing sites. Of all foreign firms that are inspected,
thirty-four percent are not in compliance. The agency is reviewing its findings of the past few years in hopes of instituting a more effective strategy for dealing with foreign companies that do not maintain compliance.

One such strategy is a Memorandum of Understanding (MOU) with a foreign government. The FDA recently signed such an agreement with Russia. Under the MOU, Russia is to rely on the FDA's approval, inspection, and enforcement systems for U.S. drugs sold to Russia. Although some in the industry are skeptical, this will no doubt be a huge boon to U.S. pharmaceutical manufacturers; Russia has annual drug sales of greater than $300 billion, and previously only a very small percentage of U.S. drugs had penetrated that market. The FDA is seeking to expand MOUs to foodstuffs in Russia and to negotiate MOUs with other members of the former Soviet Union.

Under these unilateral agreements, the FDA's involvement in the regulation of foreign drug industries increases rather than decreases. Although an MOU gives the FDA legal authority to rely on inspections conducted by the foreign country, an MOU is often established because the foreign country lacks the expertise to ensure that FDA standards are implemented. For the MOU with Russia, for example, the FDA must train Russian inspectors to use FDA methods and information systems.

The FDA prefers to negotiate MOUs on its own terms rather than rely on international efforts to harmonize inspection and enforcement. The agency obviously does not feel bound by international harmonization agreements. The Deputy Director of the FDA Office of Enforcement has stated, "the FDA does not need to use international standards if it feels they do not ensure adequate consumer protection. Such standards include Codex and ISO [9000]."

Presumably, such standards would also include the EU's mark of

136. Shroff, supra note 125, at 578.
137. Id. at 578-79.
138. Id. at 578. The FDA also has partial MOUs with Switzerland, Sweden, Canada, and Japan. Relihan, supra note 112, at 257-58 n. 214.
139. Shroff, supra note 125, at 578.
140. Vogel, supra note 6, at 20-21.
141. Shroff, supra note 125, at 578.
142. Contrera, supra note 11, at 949.
143. Contrera, supra note 11, at 949; Relihan, supra note 112, at 257.
144. Shroff, supra note 125, at 578.
145. See id. at 578-79
146. Id. He also stated that "NAFTA does not require the agency to do anything differently than
quality for medical devices, the "CE" Mark. Another unsettling aspect of the FDA's power over foreign drug manufacturing is that when the agency denies admission into the United States, a foreign drug manufacturer has no right to judicial review of the decision.

The FDA would prefer that it, and not the ICH, be in charge of harmonizing certain inspection procedures. "We believe we could find perhaps a better venue that is more broadly-based worldwide" to foster discussion of GMP harmonization. The FDA has been negotiating a GMP agreement with the EU to "harmonize" their inspection processes. The agreement is not as broad as the MOU with Russia, but it would guarantee the FDA access to the Member States' inspection reports as well as give the FDA the right to conduct its own inspections in the Member States. Currently, the FDA must seek permission before conducting a foreign inspection.

According to FDA Commissioner David Kessler, the FDA has priorities other than working with ICH on international harmonization. Before ICH2, he noted that, "it is possible that the FDA will not be able to move ahead on some ICH projects with the sense of urgency they may deserve. . . . [W]e have


148. Hyman, supra note 131, at 529.


150. Id.

151. Id.

152. Pharma Harmonization "Helps Patients," Says ICH, supra note 24. Some have argued against FDA participation in the ICH process because they fear a "race to the bottom" resulting in a lowering of FDA standards. Contrera, supra note 11, at 951-52.
to adjust our contribution to our means.”

Mostly, FDA employees work on ICH matters “in addition to their other responsibilities.” Congress is in full control of the FDA, with all the political discretion that implies. The FDA may not deviate from congressional policy without authorization in the form of legislation. Many in the FDA feel that harmonization efforts detract from the agency’s primary goal of drug review.

A re-invigorated FDA enforcement division could decrease competition in the marketplace in two ways. First, drug firms will have to maintain even more extensive and costly in-house quality assurance and legal defense programs. Second, if the penalties for non-compliance are too high (or too numerous), drug firms, even highly reputable firms, literally will not be able to afford mistakes. While some firms undoubtedly should be eliminated from the market because their products are unsafe, the real question for enforcement is the same as for the approval process: Are the standards too high? Instead of questioning the enforcement system at its fundamental, scientific level, the FDA has merely improved the mechanics of the system. Coupled with an expanded review staff, this does not bode well for the efforts of the ICH.

IV. OTHER BARriers TO INTERNATIONAL HARMONIZATION

In addition to the obstacles previously discussed, there remain a number of difficulties which must be addressed before a truly global pharmaceutical market can be achieved. Not all of these problems can be resolved by the ICH. So far, ICH has limited itself to only the scientific aspect of drug regulations. Thus, most of these other issues will have to be addressed by other multinational cooperative bodies, or perhaps by the national political entities.

153. *Pharma Harmonization “Helps Patients.” Says ICH, supra note 24. See also Contrera, supra note 11, at 952 (referring to FDA Task Force Study which concluded that FDA resources were not adequate to conduct international activities).


155. See statement of Fred W. Lyons on behalf of Pharmaceutical Research and Manufactures of America before the Commerce Committee. *FDA Approval Process, FEDERAL DOCUMENT CLEARING HOUSE, INC., May 1, 1996, available in 1996 WL 10163340 (stating that the FDA has been the most studied agency over the years).

156. Beckner, supra note 114, at 539.

157. Contrera, supra note 11, at 953.

158. See generally U.S. DEPT. OF JUSTICE, supra note 130 (discussing criminal prosecution of corporate officials).
One major barrier to international harmonization is the huge cultural difference between the East and the West. Compared to Western countries, Japan and other Asian countries have very different philosophies about medicine, health, and doctors. Western manufacturers have resisted conducting clinical trials in Japan because doctors there are frequently unwilling to follow the protocols precisely. This leads to skewed and unreliable data. Another cultural difference is the unwillingness of Americans to accept any level of risk when it comes to pharmaceutical products. Surely the American people must bear some of the responsibility for the inordinately high standards imposed by the FDA.

International harmonization proponents also cannot ignore that issues affecting pharmaceuticals are often political and social, not just scientific or economic. The regulation of drugs is virtually synonymous with notions of national sovereignty. In Europe, it is said that “pharmaceuticals and politics go together.” The same can be said of the American and Japanese drug industries. The drug industry has strong ties to cultural and societal norms concerning public health and safety, to the agencies responsible for the evaluation of new drugs, and to various special interest groups of professionals and consumers. These forces frequently pull the industry in different directions, both within a single country and across the international scene. ICH only directly addresses the harmonization of products and clinical practices, not the regulatory agencies, which are subject to intense politicizing in all the countries involved. It is unclear how much harmonization is possible without successfully integrating the various forces that influence the industry.

Another barrier to harmonization is the notion that success must be measured by a resulting decrease in the cost of drugs—either to the consumer, the manufacturer, or both. It is true that ICH1 and ICH2 reduced some decidedly overzealous testing during a new drug’s early stages. Most of the costs associated with drug development occur, however, in the later stages of development.

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160. 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.


162. Orzack et al., supra note 38, at 852.

163. *Id.*

164. *Id.* at 847.

165. Some commentators have argued that the advances of ICH1 and ICH2 will reduce the cost of developing new drugs. Contrera, supra note 11, at 953.
testing, the human clinical trials. Also, considering that the FDA may define
the quality of drug manufacturing and that the Japanese will likely set the
standards for drug testing, it is almost certain that the harmonization process
will raise international standards166 and increase costs to the industry and to the
consumer.

It is not certain that international harmonization will ever decrease costs. A
well known study conducted by Professor Sam Peltzman, and updated
recently by Robert Hahn and John Hird, estimated that FDA regulations give
rise to a "dead weight loss" of up to three billion dollars a year.167 Moreover,
with each major new piece of FDA legislation in the United States, the average
review time for approval of new drugs increased dramatically.168 The industry
and the public need to realize that, even if ICH succeeds, it will be only a small
part of the solution.

The problem is exacerbated because international harmonization requires
symmetry, and ironically the pharmaceutical industry is incredibly diverse and
driven by notably asymmetrical forces. There are a few very large players, but
there are literally thousands of smaller "boutique" drug firms.169 Europe alone
has more than 2000 drug companies and seven of the world's top ten
pharmaceutical firms.170 Large companies have a distinct advantage over
smaller competitors.171 For example, the large players can afford to devote
significant manpower to international issues such as licensing, certification,
and distribution agreements.172 Another advantage is that many large
pharmaceutical companies established European and American subsidiaries
long ago, and now these subsidiaries play a very important role in overall
company performance.173 The organization, reputation, effectiveness, and
procedures of these companies all have significant national differences.

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166. In fact, it is the intention of the FDA to raise the ICH standards. Id. at 951-53.
167. Beckner, supra note 114, at 530. "Dead weight loss is '[a] measure of efficiency loss, given
by the sum of lost consumer and producer surplus."
Id. at 529 n.14 (quoting RUBIN, PINDYCH & DANIEL
168. Id. at 531.
169. In Germany, there are 600 pharmaceutical firms, and 2/3 of them are small, national companies.
Orzack et al., supra note 38, at 848.
in 1995 WL 2153139.
171. Gomez, supra note 4.
172. Id.
173. Id.
Formulating policies and promulgating regulations to monitor all aspects of the entire industry is "at best uncertain."\footnote{174} One of the main obstacles to a true world market is the great disharmony of patent laws around the world.\footnote{175} There is strong evidence that the vitality of any modern health care system is directly dependent upon a strong intellectual property regime.\footnote{176} The European biotechnology industry suffered a major blow in March 1995 when the EU rejected the Biotechnology Patent Directive, which would have permitted the patenting of certain life forms.\footnote{177} The directive would have allowed the EU to compete more effectively with American and Japanese drug companies that already enjoy significant legal protection in their respective countries.\footnote{178}

As with any international agreement, ICH needs to maintain a clear focus on its original goals. Early successes of the ICH and the recognition of a great need for international cooperation have led some to advocate a type of "mission creep."\footnote{179} 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

\footnotesize{\begin{itemize}
\item[174.] Orzack \textit{et al.}, \textit{supra} note 38, at 848.
\item[175.] Although the General Agreement on Tariffs Treaty is expected to alleviate some of the problems associated with patent laws in a world market, countries are allowed a generous transition period before pharmaceuticals will be effectively protected against product infringement and unequal treatment. \textit{TRIPs Transition Period "Far Too Long": IFPMA, MARKETLETTER, May 22, 1995, available in 1995 WL 2152927.} For an analysis of the global harmonization of patent law, see Anthony Sabatelli & J.C. Rasser, \textit{Impediments To Global Patent Law Harmonization}, 22 \textit{N. KY. L. REV.} 579 (1995).
\item[176.] Although India is plagued with recurrent health epidemics of easily treatable diseases, manufacturers have avoided that country because of poor patent protection. \textit{See Indian Industry Seminar Discusses Patents, MARKETLETTER, May 22, 1995, available in 1995 WL 2152963.} Even though China represents more than 22\% of the world's population, manufacturers had also previously avoided China, until it agreed to increase enforcement of intellectual property rights. \textit{US Industry Welcomes China Trade Treaty, MARKETLETTER, Mar. 6, 1995, available in 1995 WL 2151973.} Problems even exist among developed countries. For example, some countries have attempted to exploit their participation in the Human Genome Project by trying to patent identified gene sequences. Barbara Looney, Note, \textit{Should Genes be Patented? The Gene Patenting Controversy: Legal, Ethical, and Policy Foundations of an International Agreement}, 26 \textit{LAW \\& POL.'Y INT'L BUS.} 231, 245 (1994).
\item[178.] \textit{Id.}
\item[179.] Mission creep occurs when an organization's original objectives shift and expand to include less focused and less realistic goals.
\end{itemize}}
level of regulatory scrutiny as the pharmaceutical industry.\textsuperscript{180} This is entirely beyond the scope of ICH goals.

One possible solution to mission creep is for the ICH to limit its efforts even further, concentrating on only one or two classes of drugs until the problems have been resolved.\textsuperscript{181} ICH could follow the lead of the EU's concertation procedure and focus on harmonizing only the regulatory apparatuses for medical products derived from biotechnology or high technology. This would not solve all the problems, since every class of drugs may present its own particular set of difficulties, but it would allow some breathing room to resolve the major conflicts. Since the ICH is intended to be the first step in a long and continuous process, a gradual approach may be the best approach.

CONCLUSION

Globalization of drug industry regulation promises to radically change the way consumers, manufacturers, and governments think and act toward health care. ICH is a small step in the right direction for the pharmaceutical world, but the benefits may not be as great as hoped. As this article suggests, it will unfortunately be very easy for ICH to get sidetracked or derailed. The EU is struggling to standardize the drug regulatory process within its borders, among countries already committed to a "borderless society" in all other respects. If they cannot succeed in creating a harmonized pharmaceutical regulatory system, the future for a worldwide system looks dim indeed. The FDA, convinced that the U.S. system is best, seems intent on harmonizing the world one country at a time. It is hoped that harmonization efforts will proceed along the road that leads to an increase in drugs that are less expensive to make and easier to market. It is more likely, however, that efforts to harmonize will exacerbate current regulatory problems and create a whole crop of new ones.


\textsuperscript{181} This does not seem likely since the FDA recently agreed to include the U.S. generic industry in ICH talks. Previously, ICH guidelines were to apply only to new drugs, but it has expanded to include basic drug quality issues. \textit{US Generic Industry Wins Role at ICH, MarketLetter}, Apr. 8, 1996, available in \textit{1996 WL 9648291}. 