



THE NEED FOR COMPREHENSIVENESS AND INCREASED ENFORCEABILITY IN THE STANDARDIZATION OF INTERNATIONAL PHARMACEUTICAL REGULATIONS

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THE NEED FOR COMPREHENSIVENESS AND INCREASED ENFORCEABILITY IN THE
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THE NEED FOR COMPREHENSIVENESS AND INCREASED ENFORCEABILITY IN THE STANDARDIZATION OF INTERNATIONAL PHARMACEUTICAL REGULATIONS

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THE NEED FOR COMPREHENSIVENESS AND INCREASED ENFORCEABILITY IN THE STANDARDIZATION¹ OF INTERNATIONAL PHARMACEUTICAL REGULATIONS

I.

INTRODUCTION

Sovereign nations have the responsibility to protect the health and well-being of their constituents. This responsibility manifests itself in an often staunch defense of national pharmaceutical regulations, developed to protect citizens from unsafe products. However, differences in regulatory systems across countries create barriers to trade in pharmaceuticals. As the world becomes increasingly interconnected, barriers to trade seem increasingly anachronistic. The economic and social benefits from reducing impediments to inter-nation trade are indisputable. This principle holds true for the pharmaceutical industry, in which liberalization would produce enormous benefits for industry and consumer alike. In recognition of the benefits of internationalization, many nations are moving towards eliminating non-tariff barriers to trade through standardization of their pharmaceutical regulatory systems.

This article will discuss the main mechanisms by which the United States and other countries are attempting to standardize their pharmaceutical regulations. I first explore the need for standardization and the potential

¹The word more commonly used to include all the mechanisms to be discussed, “harmonization,” has different meanings for different people in the pharmaceutical arena. For example, some people use “harmonization” interchangeably with “mutual recognition agreements,” a mechanism which I will discuss separately. See Barbara Indech, *The International Harmonization of Human Tissue Regulation: Regulatory Control over Human Tissue Use and Tissue Banking in Select Countries and the Current State of International Harmonization Efforts*, 55 **Food & Drug L.J.** 343, 366 (2000). Others use “harmonization” to refer to all mechanisms of aligning country regulatory practices, while still others use “harmonization” as a distinct mechanism alignment. I use the word “standardization” to include all the mechanisms to be discussed to avoid the confusion that may result from the use of a term with no standardized definition.

benefits that standardization offers. Then I sketch the early efforts of nations to move toward standardization. I present and critique the mechanisms by which standardization is currently proceeding and the progress that has been made to date. I also detail the Food and Drug Administration's (FDA) participation in international standardization.

I argue that reform of the standardization process is necessary to reap the full benefits of standardization. Specifically, the various tools of standardization, the ICH, MRAs, and MOUs need to be integrated so as not to work at cross-purposes. The standardization process must be expanded to account for the views of consumers and non-member nations. Most importantly, in the absence of a way to bind nations to commitments to standardize pharmaceutical regulations, standardization mechanism are in danger of becoming another layer of regulatory delay; to avoid this pitfall, standardization agreements must be made enforceable.

II.

BACKGROUND

A.

The Need for Standardization

Standardization of pharmaceutical regulations will benefit consumers and producers alike, by bringing effective treatments to market faster and reducing the costs of drug development. Developing a drug for marketing is an extraordinarily costly process, both in money and time. One estimate places the average costs to develop a prescription drug at an average of \$802 million.² Bringing a drug to market takes between

²See Tufts Center for the Study of Drug Development, *Tufts Center for the Study of Drug Development*

ten and fifteen years in the United States.³ The rising costs of drug development have been attributed to spiraling clinical trial costs.⁴

Historically, each country has had its own standards for regulating pharmaceuticals marketed in that country. The FDA for example, requires several phases of testing, as laid out in the Federal Food, Drug, and Cosmetic Act (FDCA), before allowing a drug to be sold to the public.⁵ Individual countries often require that domestic legal and regulatory standards be met even if a drug is already widely marketed in another or several other countries.⁶ Thus, for the FDA to approve a drug for use in the United States, a domestic investigator must sometimes replicate the results of experiments already conducted in the drug's country of origin.⁷ Such requirements necessitate that a drug undergo expensive and time-consuming clinical trials to satisfy each agency from which approval is sought.⁸

Pegs Cost of a New Prescription Medicine at \$802 Million, News Release (November 30, 2001), at www.tufts.edu/med/csdd/images/NewsRelease113001pm.pdf, visited on March 10, 2002. This study updates one done ten years ago, in which costs of bringing a drug to market averaged \$231 million in 1987 dollars. Had inflation been the only cause of increased cost, the amount to bring a drug to market would be \$318 million in 2000 dollars. *See Id.*

³*See id.*

⁴*See id.* The Tufts Center study found that while costs increased in inflation-adjusted terms for all R&D phases, there were particularly dramatic increases for the clinical period. The inflation-adjusted annual growth rate for capitalized clinical costs (11.8%) was more than five times greater than that for pre-clinical R&D. *See id.*

⁵*See* Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §301 et seq (1999). To be marketed in the United States, a drug must be approved by the FDA after review of a New Drug Application (NDA). The NDA must include the results of at least two controlled clinical trials. In the NDA, proposed labeling must be supported by data showing the safety of the recommended uses and any potential side effects or contraindications associated with usage of the drug. Post-marketing reports of any adverse reactions must be submitted to the FDA periodically, and manufacturing plants are subject to FDA inspection. *See* Thomas M. Moore and Siobhan A. Cullen, *Impact of Global Pharmaceutical Regulations on U.S. Products Liability Exposure*, 66 **Def. Couns. J.** 101, 102-103 (1999).

⁶However, developing countries usually accept approvals from the United States and other developed countries.

⁷*See* 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, 205 (1997). However, the FDA now does approve some drugs based on foreign trials. *See* Eric M. Katz, *Europe's Centralized New Drug Procedures: Is the United States Prepared to Keep Pace?* 48 **Food & Drug L.J.** 577, 581 (1993). 21 CFR §312.120(a) states that the FDA accepts foreign clinical studies not conducted under an IND as long as they are "well designed, well conducted, performed by qualified investigators, and conducted in accordance with ethical principles acceptable to the world community." 21 CFR §312.120. §312.120(b)-(c) set out the information to be submitted to the FDA in order to rely on foreign studies to support an application. However, if marketing approval of a new drug is to be based solely on foreign clinical data, §314.106 states that approval may be granted only if "(1) The foreign data are applicable to the U.S. population and U.S. medical practice; (2) the studies have been performed by clinical investigators of recognized competence; and (3) the data may be considered valid without the need for an on-site inspection by FDA or, if FDA considers such an inspection to be necessary, FDA is able to validate the data through an on-site inspection or other appropriate means." *Id.*

⁸*See* Paul M. Booth, *FDA Implementation of Standards Developed by the International Conference on Harmonisation*, 52 **Food & Drug L.J.** 203, 203 (1997).

Regulatory delays have detrimental effects on potential consumers. Economists and doctors worry that patients will not be able to gain access to life-enhancing and possibly life-saving treatments as cheaply or quickly.⁹ Patients who would be willing to take the risks and use new drugs before they are approved by the FDA lose the potential therapeutic benefits they might have received.¹⁰ Supporters of standardization see the FDA drug regulatory process as inordinately cautious and decry FDA resistance to reducing the stringency of the requirements for drug approval. After Thalimide and other disasters, the FDA developed drug regulations in deference to the public's refusal to sacrifice safety for cost effectiveness.¹¹ Critics of the FDA assert that such caution is causing more deaths than it prevents, by delaying access of Americans to life-saving drugs.¹²

However, these effects are difficult to quantify, and as such fail to spur action to the same extent as do reports of adverse effects of drugs.¹³ A study of therapeutic loss conducted over twenty years ago, concluded that the increased stringency in drug approval by the FDA after 1962 caused a decrease in drug innovation in the United States. The therapeutic loss resulting from FDA regulation was estimated at over \$450 million per year.¹⁴ More recent studies posit that regulatory delays negatively impact patient life expectancy and quality of life.¹⁵ While a drug that produced fatalities of this magnitude would be seen as catastrophic, this

⁹See Teresa Pechulis Buono, *Biotechnology-Derived Pharmaceuticals: Harmonizing Regional Regulations*, 18 **Suffolk Transnat'l L. Rev.** 133, 134 (1995).

¹⁰See Note, *FDA Reform and the European Medicines Evaluation Agency*, 108 **Harv. L. Rev.** 2009, 2013 (1995).

¹¹Michelle D. Miller, *The Informed-Consent Policy of*, 30 **Cornell Int'l L.J.** 203, 233. See id. Part I.A.2. for a more complete detailing of these pharmaceutical disasters.

¹²John Patrick Dillman, *Prescription Drug Approval and Terminal Diseases: Desperate Times Require Desperate Measures*, 44 **Vand. L. Rev.** 925, 939. May, 1991

¹³See id. at 2011.

¹⁴See id. at 2013.

¹⁵See id. at 2014. One estimate suggests that 8,000 to 15,000 patients died from gastric ulcers while the FDA was considering the NDA for misoprostol, a drug used to treat that condition. Also, in the five years in which the drug nitrazepam was approved in Britain but not in the United States, pharmacologists argue that millions of lives could've been saved. See id.

therapeutic loss has been largely ignored.

The necessity to comply with the incompatible regulations of various agencies has negative implications for industry, as well as consumers. Faced with the costs of duplicative research trials, pharmaceutical companies raise their prices, take longer to introduce drugs into the market, or choose not to enter some markets.¹⁶ Regulatory inconsistencies across countries prevent pharmaceutical companies from developing globally acceptable product designs, manufacturing processes, packaging and labeling.¹⁷ Due to the additional expense to pharmaceutical companies in complying with multiple regulatory schemes, these companies are less likely to pursue global markets.¹⁸ Further, the increased lag time between development and distribution of a product due to standards that differ across nation increases industry costs through lost sales revenue, decrease in effective patent life, lost working capital, and wages of worker hours to process multiple applications.¹⁹ Decreasing profits from drug sales reduce the incentive for multinational companies to develop new pharmaceuticals.

Ability of drugs to enter overseas markets is hampered by the need for often duplicative studies to meet the requirements of the domestic agency charged with regulating pharmaceuticals in each country. The significant up-front costs to companies of learning the distinct regulations of another market force small drug companies from developing new drugs.²⁰ Drug approval time for companies that do seek to enter foreign markets is lengthened.²¹ Furthermore, the pharmaceutical industry argues that replicating trials already conducted in a foreign country is too expensive given its doubtful value.²² Increases in international

¹⁶See Ileana 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)

¹⁷See Moore and Cullen, *supra* note 5, at 102.

¹⁸See Buono, *supra* note 9, at 134.

¹⁹See Rosemarie Kanusky, *Pharmaceutical Harmonization: Standardizing Regulations among the United States, the European Economic Community, and Japan*, 16 **Hous. J. Int'l L.** 665, 703-704 (1994).

²⁰See *id.* at 704.

²¹See Buono, *supra* note 9, at 134.

²²See Miller, *supra* note 7, at 205.

trade also strain already overextended regulatory resources.²³

Reduction or obliteration of the necessity of complying with different regulatory regimes would benefit both consumers and producers. For consumers, standardization would remove the obstacles to patients accessing affordable, effective curative treatments. Beside lowering health care costs and providing faster access for the public to new treatments, international consensus on regulations would enhance international public health as the best of each country's health system is meshed together.²⁴ Furthermore, a global response is needed since disease recognizes no national borders.²⁵ For companies, standardization will bring about greater revenue from sales of pharmaceuticals as drugs go on the market much sooner.²⁶ In the United States, if regulatory approval time is reduced by one year, drugs can generate profits three to four years earlier as the costs of maintaining a drug in the absence of profits would be decreased and profits would accrue sooner. Six months less of review time could generate savings of millions of dollars for companies that can be reinvested in research.²⁷ U.S. companies might choose to locate more manufacturing and research facilities in the United States in the absence of the myriad of regulations that have driven them overseas.²⁸ Standardization will facilitate simultaneous introduction of a new drug in various countries as well as intra-company globalization of procedures across the global organization, particularly for clinical study protocols and reports.²⁹ Regulators would be more efficient given the benefit of the experiences of their counterparts

²³ See Alexander M. Donahue, *Equivalence: Not Quite Close Enough for the International Harmonization of Environmental Standards*, 30 **Envtl. L.** 363, 366 (2000).

²⁴ See Jane E. Henney, U.S. Food and Drug Administration Commissioner of Food and Drugs, Keynote Address at the Global Harmonization Task Force Meeting in Bethesda, Maryland (June 29, 1999), available at <www.fda.gov/oc/speeches/globalharm.html> (visited March 12, 2002).

²⁵ See Dominguez-Urban, *supra* note 16, at 247. For example, when antibiotics in developing countries are used in inadequate dosages and for inadequate periods, drug-resistant strains of bacteria are created, which then spread across national boundaries. See *id.* at 249.

²⁶ See Kanusky, *supra* note 19, at 704.

²⁷ See *id.*

²⁸ See Patrick Dillman, *Prescription Drug Approval and Terminal Diseases: Desperate Times Require Desperate Measures*, 44 **Vand. L. Rev.** 925, 937 (1991).

²⁹ See Caroline Nutley, *The Value and Benefits of ICH to Industry*, 2, 5 (2000), at <http://www.ifpma.org/pdfifpma/ValueBenefits.pdf> (visited March 13, 2002).

in other countries.³⁰

Ascertaining the safety of new drugs does not require that each country maintain a disparate regulatory approval system. Rather, various mechanisms of harmonization can reduce the costs, detailed above, of multiple regulatory systems, while still ensuring consumer safety. In fact, in pressing single-mindedly for greater regulation of pharmaceuticals, consumer advocates often labor under the mistaken impression that more strictures necessarily result in increased safety. However, greater control of drug production may not improve drug safety.³¹ Standardization aims to create safer pharmaceuticals by distilling the shared wisdom of multiple regulatory systems into a more effective drug development and approval process, in which some tests might even be decreased or eliminated.³²

B.

Early Attempts at Standardization

Regulatory authorities have been under increasing pressure to standardize the drug approval process. Regulatory agencies must operate in an increasingly complex economy, one in which the health industry, and the multinational companies that dominate it, is a powerful force. Such multinational companies would prefer to submit one application to one regulatory body for approval to market a drug. The rapid pace of technological change challenges regulatory agencies to fit new models of therapeutics into existing systems.

Resource constraints in the face of new technologies require innovative solutions and collaboration on behalf

³⁰ See Henney, *supra* note 24.

³¹ See Kanusky, *supra* note 19, at 706.

³² *Id.* at 688.

of regulators. In a world in which international activities are increasingly important, collaborative strategies are becoming ever more necessary for regulators.³³

The movement towards standardization of pharmaceutical regulations was presaged by the movement to standardize food regulations. Specifically, in 1962 the World Health Organization (WHO) and the United Nations Food and Agriculture Organization (FAO) jointly established the Codex Alimentarius Commission (Codex), an international standard-setting body intended to facilitate international trade of food and to ensure that the world's food supply is sound, wholesome, and properly labeled.³⁴ All members and associate members of the WHO and FAO can become members in the Codex.³⁵ Codex sets descriptive standards for foods so that the 162 member nations all have the same understanding of what constitutes a given food.³⁶ Since its establishment, Codex has promulgated over 250 international food standards. These standards are developed by Codex's fourteen subsidiary commodities committees and eight broader committees that deal with more general subjects, such as the Codex Committee on Food Additives and Contaminants. After adoption by Codex, food standards are promoted to member nations for their acceptance.³⁷ Member countries and nongovernment organizations (NGOs) can comment freely on food standards under development in the Codex committees, allowing the food industry to work with government officials and within NGOs to forge a unified position. The structure and operating principles of Codex are reflected in the ICH.³⁸

Codex standards are not binding on member nations.³⁹ In recognition of its members' sovereignty, countries

³³See *Therapeutic Products Programme's International Strategy, Key Trends Shaping the Current International Environment*, at http://www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/strategy/int-stra_e.html (visited January 27, 2002).

³⁴See Lucinda Sikes, *FDA's Consideration of Codex Alimentarius Standards in Light of International Trade Agreements*, 53 **Food & Drug L.J.** 327, 328 (1998).

³⁵See John S. Eldred and Shirley A. Coffield, *What Every Food Manufacturer Needs to Know: Realizing the Impact of Globalization on National Food Regulation*, 52 **Food & Drug L.J.** 31, 31-32 (1997).

³⁶See Sikes, *supra* note 34, at 328.

³⁷See Eldred and Coffield, *supra* note 35, at 32.

³⁸See text pp. 38-40. For a detailed description of the Codex process for promulgating standards, see <http://www.fsis.usda.gov/OA/codex/operate.htm>, visited on March 11, 2002.

³⁹See Sikes, *supra* note 34, at 328.

are allowed to decide what parts of the international standards, if any, they will adopt, with Codex membership entailing no obligation to follow any Codex standard or guideline.⁴⁰ For example, the FDA does not view the Codex standards as binding safety standards.⁴¹ Nonetheless, the U.S. Codex, the organization comprising government officials from the U.S. Department of Agriculture, the Food and Drug Administration (FDA), and the Environmental Protection Agency which manages and implements United States involvement in Codex, aims to strengthen Codex as a means of fostering adherence to Codex standards to realize the economic benefits of standardization.⁴²

In a recent change in policy, Codex standards have been given “teeth.” Members of the World Trade Organization (WTO) are now obligated to incorporate Codex food standards into their national regulations and such standards are persuasive authority under the WTO dispute resolution structure.⁴³ Member nations are allowed to develop more stringent requirements than those proposed by Codex, but these standards may be challenged under the WTO as disguised trade barriers.⁴⁴

Other than Codex, various multilateral efforts to regulate the food supply set the precedent for international cooperation that ultimately spread to the pharmaceutical industry. For example, in an attempt to address common problems, FDA officials met semiannually in the 1970s with representatives of the regulatory bodies of Canada and Britain to discuss problems facing one country that for which the other countries might be at risk. These discussions led to some collaborative attempts to deal with shared threats. One such collab-

⁴⁰See Eldred and Coffield, *supra* note 35, at 34.

⁴¹21 C.F.R. § 130.6 (a), Review of Codex Alimentarius food standards, states that “[a]ll food standards adopted by the Codex Alimentarius Commission will be reviewed by the Food and Drug Administration and will be accepted without change, accepted with change, or not accepted.”

⁴²See Eldred and Coffield, *supra* note 35, at 32. The US Codex generated a Strategic Plan asserting that: 1) The United States should support the efforts of the Codex and other international organizations to improve the scientific basis for Codex standards, so that these standards may be based consistently on sound scientific analysis and evidence; 2) the United States should support efforts to improve Codex management processes in order to enhance the Commission’s credibility with national regulatory authorities and consumers; 3) the United States should step up its commitment to systematically and routinely evaluate Codex standards for acceptance as the basis for U.S. standards; 4) the U.S. Codex should encourage and enable all significantly interested nongovernmental bodies to participate actively in Codex activities; and 5) the U.S. Codex should be allocated sufficient resources to effectively carry out its mission. See Office of the U.S. Coordinator for Codex Alimentarius, U.S. *Codex Strategic Plan (Draft Plan)*, ii-iii (1995).

⁴³See Eldred and Coffield, *supra* note 35, at 33.

⁴⁴See *id.* at 34.

oration was the joint effort to evaluate a Canadian study on saccharine.⁴⁵

Likewise, the common nature of many issues involved in drug regulation led to similarities in solutions across countries even prior to formal standardizations attempts. Specifically, all countries needed to respond to public pressure for increased speed in getting effective and safe treatments to those in need in the face of rising drug development and research costs.⁴⁶ Subject to these conditions, decisions that regulatory regimes in all countries need to make include: how to balance increased speed of approval with protecting the public against potential hazards; whether to focus on safety and innovation or on proven efficacy; and whether to measure value of a drug in terms of clinical benefits or a narrower evaluation of factors such as cost-effectiveness or protection of domestic producers.⁴⁷

Although not necessarily to the same degree, all countries have to deal with the abovementioned issues, with the likelihood that they will gravitate toward some similar solutions.⁴⁸ This remains true even though an issue of particular prominence in one country may be faced to a lesser degree by other countries' regulatory bodies. For example, Japan focused on fostering innovation and attention to physiologic distinctiveness; the U.K. has been concerned with regulatory secrecy and conflicts of interest; the United States has had particular problems with the demands of political constituencies and balancing rapid approval with societal safety; and France has had to deal with the treatment of alternative medicines and the impact of regulations on local industry.⁴⁹ An example of the arrival at similar solutions to a similar problem despite differential emphases includes the FDA's fee structure to make drug registration applicants fund their own registration process.⁵⁰ Such a system is similar to the United Kingdom institution of self-financing regulatory agencies

⁴⁵See Richard A. Merrill, *FDA and Mutual Recognition Agreements: Five Models of Harmonization*, 53 **Food & Drug L.J.** 133, 133 (1998).

⁴⁶See Indech, *supra* note 1, at 368.

⁴⁷See Bryan L. Walser, *Shared Technical Decisionmaking and the Disaggregation of Sovereignty: International Regulatory Policy, Expert Communities, and the Multinational Pharmaceutical Industry*, 72 **Tul. L. Rev.** 1597, 1640-1641 (1998).

⁴⁸See *id.* at 1642.

⁴⁹See *id.*

⁵⁰See *id.*

(sefras), agencies licensed by government that make regulation a business by charging those regulated for their regulation services.⁵¹

The process of similar solutions developing in response to similar problems is self-reinforcing.⁵² Once similar solutions are chosen, the divergence between the regulatory regimes in different countries is reduced. Countries with more convergent background regimes as the context for regulatory decision-making are even more likely to make similar choices.

Early attempts at more formal standardization were propagated by regional alliances. The Council of Europe and the Organization for Economic Cooperation and Development (OECD) have supported pharmaceutical standardization.⁵³ The Council for Mutual Economic Assistance, the European Free Trade Area, and the Nordic Council of Medicines each created shared testing and evaluation guidelines.⁵⁴ From 1973 to 1978 Belgium, Luxembourg, and the Netherlands instituted a common system of drug registration, an experiment that encouraged pharmaceutical companies to advocate increasingly for standardization of regulatory regimes.⁵⁵

More than any other step toward standardization, EC legislation on pharmaceuticals represented multi-country regulatory consensus and demonstrated that such consensus was possible.⁵⁶ The EU had been working toward a common regulatory process for drugs as early as 1965.⁵⁷ In 1965, directive 65/65 set the stage for automatic mutual recognition of national drug marketing authorizations among member European states. Action on the directive occurred in 1975, with the establishment of the Committee for Proprietary

⁵¹See *id.*

⁵²See Walser, *supra* note 47, at 1642.

⁵³See Kanusky, *supra* note 19, at 688.

⁵⁴See *id.*

⁵⁵See *id.*

⁵⁶See *A Brief History of ICH*, at <http://www.ifpma.org/ich8.html> (visited on March 16, 2002).

⁵⁷See Walser, *supra* note 47, at 1661.

Medicinal Products (CPMP). The CPMP created a multi-state procedure for drug approval, in which the CPMP served as a central clearinghouse for drug approvals submitted by any of the twelve member states of the European Economic Union to any single European State. After approval was sought in any single state, application could be made to as many as five states within the Union, and those States were required to consider the approval in the initial state in conducting their own reviews.

However, because each state could reject a drug despite approval by the initial state of submission and almost all submissions were denied general approval due to objections from member states, the CPMP system effectively added another layer of approval without any apparent benefit in expediting market access.⁵⁸ Changes to the CPMP system, allowing drug companies to apply for approval in a single and the CPMP simultaneously, with applications to additional states granted unless the other states responded negatively within ninety days, failed to remedy the situation of mutual distrust and stalemate.⁵⁹

Real progress toward European mutual recognition only came with the 1987 centralized procedure for the approval of biotech products, followed by the 1993 provisions of the European Commission authorizing the creation of a European Agency for the Evaluation of Medicinal Products (EMA). The EMA was endowed with the power to grant marketing authorizations valid throughout the EU.⁶⁰ The EMA coordinates the approval, manufacturing and inspection of medicines between the CPMP and regulatory bodies of member states. Requests to the EMA are forwarded to the CPMP, which issues an opinion within 210 days, subject to the affirmation of the European Commission's Standing Committee on Medicinal Products for Human Use. By allowing the acceptance of the CPMP to become final unless the European Council acts within ninety days of a rejection by the Standing Committee, the system facilitates approval and rejection by indi-

⁵⁸See David V. Eakin, *The International Conference on Harmonization of Pharmaceutical Regulations: Progress or Stagnation?* 6 **Tulsa J. Comp. & Int'l L.** 221, 224 (1999).

⁵⁹See *id.*

⁶⁰See Walser, *supra* note 47, at 1661-3.

vidual member states is precluded.⁶¹

However, the legislatures of each member state have never been bound by EMEA decisions.⁶² National legislatures cannot be bound by the decisions of the CPMP and the European Commission, which seriously impedes the success of the system in reducing inspections and decreasing time to market.⁶³

Other than the EU standardization process, other early steps toward multinational pharmaceutical regulatory cooperation were often bilateral, in the form of MOUs between two countries or organizations. Agreements on good manufacturing practices existed in the late 1980s between the FDA and Switzerland, the FDA and Sweden, and the FDA and Canada, and the FDA had separate agreements on good laboratory practices with Canada, Sweden, Switzerland, West Germany, France, Italy, the Netherlands, and the United Kingdom.⁶⁴ In 1990, talks began between the FDA and the European Commission on good manufacturing and laboratory practices applicable to EC members and the United States.⁶⁵

After 1991, standardization attempts expanded into multilateral efforts. In February 1991, at the Joint Pharmacopeial Open Conference on International Harmonization of Excipient Standards, sponsored by the United States, British, European, and Japanese Pharmacopeias, participants advocated for uniform regulation of excipients.⁶⁶ Harmonization of health care product naming was the goal of a November 1991 conference sponsored by the United States, the EC, and Canada.⁶⁷

Attempts at establishing global standards for pharmaceuticals were spurred in part by efforts at reducing barriers to global trade in general. In the past, eradicating trade barriers such as tariffs and quotas was the main concern. Although these trade barriers have not been completely eliminated, the focus in international trade has shifted in part to other barriers to trade, such as domestic production and manufacturing stan-

⁶¹ See Eakin, *supra* note 58, at 225.

⁶² See *id.*

⁶³ See *id.* at 225-226.

⁶⁴ See Kanusky, *supra* note 19, at 689.

⁶⁵ See *id.* at 688-689.

⁶⁶ See *id.* at 689.

⁶⁷ See *id.*

dards. These standards encompass rules set voluntarily by industry and mandatory government guidelines, both of which are enforced by conformity assessment bodies, either private or governmental, to certify that the standards are being met.⁶⁸ In many ways, the multilateralization of standards is the natural next step in eliminating barriers to trade, as the cost of compliance with domestic standards and conformity assessment procedures can be as prohibitive to international trade as tariffs.⁶⁹

International agreements, such as the North American Free Trade Agreement (NAFTA) (1993) and the Uruguay Round of the General Agreement on Tariffs and Trade (GATT) (1994), which established the World Trade Organization (WTO), significantly advanced the movement toward uniform global standards, by moving beyond routine tariff-reduction measures.⁷⁰ NAFTA and the WTO are permanent institutional structures which address issues like domestic public health, food safety, consumer, worker and environmental protection policies of member, all traditionally the purview of domestic government; as such, these bodies go far beyond ordinary trade agreements focusing on tariffs and quotas.⁷¹ These agreements address the establishment of domestic standards, with the intent of preserving the ability of a government to set national standards, while preventing the use of such standards to favor domestic products unfairly.⁷² The WTO addresses this issue in its Agreement on Technical Barriers to Trade, and NAFTA does so in Chapter Nine on Standards-Related Measures.⁷³ Both restrict the domestic policy aims that member countries may follow, as well as the tools to be used in implementing even acceptable domestic policy.⁷⁴ Both agreements recognize the right of countries to implement standards viewed as appropriate for the protection of public health, safety,

⁶⁸See Allyson L. Senie and Kathryn E. Helne, *Developments in the Multilateral Treatment of Standards*, 1075 **PLI/Corp** 221, 224 (1998).

⁶⁹See *id.* at 223-224.

⁷⁰See *Accountable Governance in the Era of Globalization: the WTO, NAFTA, and International Harmonization*, at <http://www.harmonizationalert.org/HarmBackgrounder.htm> (visited January 14, 2002).

⁷¹See *id.*

⁷²See Senie and Helne, *supra* note 68, at 226-227.

⁷³See *id.* See http://www.wto.org/english/docs_e/legal_e/final_e.htm (visited March 17, 2002) for the full text of the Agreement on Technical Barriers to Trade and <http://www.mac.doc.gov/nafta/ch09.htm> (visited March 17, 2002) for the full text of Chapter Nine of NAFTA on Standards-Related Measures.

⁷⁴See *Accountable Governance*, *supra* note 70.

and the environment, provided that such standards will not be used to create unnecessary impediments to trade. Unnecessary obstacles are assumed when standards making procedures are not open and transparent; do not provide for public notice or comment by interested parties; do not involve publication of the final standard; and fail to establish a method by which affected parties can ascertain the standards relevant to a given product. Both also require and create feedback mechanisms on the effectiveness of the agreements.⁷⁵ In making inroads on standardizing what had previously been almost untouchable as exclusively within the domain of domestic regulation, NAFTA and the WTO set the stage for the standardization movement in the regulation of pharmaceuticals.

II. TOOLS OF STANDARDIZATION

There are various models by which countries may standardize their drug approval regimes, as well as various mechanisms that can be adapted within the models to further standardization.⁷⁶ These models include: 1) the agent-in-place model, in which a country is the recipient of a trading partner's development work and the country's regulatory body relies on that information to assess compliance with U.S. law; 2) the enforcement discretion model, in which the benefit of the doubt, in the form of lessened scrutiny, is granted to products of a country whose domestic regulatory requirements are deemed to be reliable; 3) the deputy

⁷⁵See Senie and Helne, *supra* note 68, at 227-228. A Committee on Standards Related Measures (CRSM), composed of government representatives from each party, implements the requirements of the standards chapter under the NAFTA agreement. This Committee on Standards includes four subcommittees, each dealing with the harmonization of standards in either the transportation, telecommunications, automobiles, or textile and clothing labeling sectors. The TBT Agreement establishes a Technical Barriers to Trade Committee, consisting of representatives from each WTO member, so as to give members the chance to communicate on matters relating to the TBT. The TBT Committee recently finished its first triennial assessment of the Agreement's operation. *See id.*

⁷⁶See Indech, *supra* note 1, at 367.

sheriff model, in which one country's regulatory agency commits to accept another's verification of the first country's domestic requirements;⁷⁷ 4) the equivalence model, in which a state accepts, in place of its own standards, the regulatory requirements of another state;⁷⁸ and 5) the harmonization model, in which all involved countries simultaneously modify their regulatory requirements such that a common approach results.⁷⁹ All of these models play a role in the efforts toward standardization.

Instruments which further these models include harmonization agreements, equivalence agreements, mutual recognition agreements (MRAs), exchanges of letters, memoranda of understanding (MOUs), and procedural agreements.⁸⁰ In harmonization agreements, countries test products to the same international standards, such that further testing is not required.⁸¹ The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), which will be discussed in depth later, is one such agreement. The member countries under the ICH still maintain their own approval processes though.⁸² Under equivalence agreements different regulatory systems are deemed equivalent by the parties, despite not being identical.⁸³ In MRAs, regulatory standards of an exporting country, although different from that of the importing country, are considered acceptable to the importing country if certain conditions are met.⁸⁴ No further testing would then be required upon importation from that country. Exchanges of letters set out only the actions to be carried out by the letter's signatory.⁸⁵ They are used instead of formal agreements when the actions to be taken are not significant enough for a formal agreement and require

⁷⁷For example, the United States would agree to accept another country's verification that goods made in that country comply with United States' law. While the substantive law to be applied is unchanged, the other country's agent is deputized to apply the law. See Merrill, *supra* note 45, at 135-136.

⁷⁸In other words, the standards of the two countries are deemed functionally equivalent. See *id.*

⁷⁹See *id.*

⁸⁰See Practising Law Institute, *The Commerce Department Speaks on International Trade & Investment, Developments in the Multilateral Treatment of Standards*, 1075 **PLI/Corp** 221, 225-226 (1998).

⁸¹See *id.*

⁸²See Linda Horton, *Mutual Recognition Agreements and Harmonization*, 29 **Seton Hall L. Rev.** 692, 717 (1998).

⁸³See Practising Law Institute, *supra* note 80.

⁸⁴See *id.*

⁸⁵See Department of Health and Human Services, *International Memoranda of Understanding; New Compliance Policy Guide; Availability*, 60 **FR** 31485, 31486 (1995).

only limited resource expenditure.⁸⁶ MOUs, as discussed later, come in various forms and can be shaped in various ways to meet the needs of the situation. Procedural agreements call for adherence to certain processes when developing regulatory standards, regardless of lack of agreement on the resultant substantive standards.⁸⁷

Each instrument may be adopted in a range of manners, allowing for use in adherence with various models of standardization. For example, the United States uses MRAs in furthering the equivalence model by requiring equivalence prior to mutual recognition.⁸⁸ However, MRAs could be structured to require recognition of another country's work without equivalence, adhering to the agent-in-place model of standardization.

Over the course of the ongoing drive towards standardization, all of these instruments have been used. Use of one instrument embodying a distinct model of standardization has not meant the exclusion of other instruments embodying different models of standardization. For example, even while the ICH was being developed, in 1994 the United States announced the conclusion of an MOU with Russia effectively making the FDA the regulatory body for pharmaceuticals in Russia.⁸⁹

All of these instruments may be used both to arrive at stricter or looser standards. Under full harmonization, all countries may agree on standards that are in line with the country with the most stringent regulatory regime, the least stringent regulatory regime, or anywhere in between. Similarly, at what point the threshold for equivalence is set will determine the rigor of the resulting regulatory regime. However, with equivalence agreements there is the danger that a less strict regime that is deemed equivalent will serve as a means for pharmaceutical producers to avoid the more rigorous controls in place in other countries, weakening the

⁸⁶ See *id.* As an example, an exchange of letters could cover an understanding that agencies will swap documents available on request to members of the public. See *id.*

⁸⁷ See Practising Law Institute, *supra* note 80.

⁸⁸ See Indech, *supra* note 1, at 367.

⁸⁹ See Walser, *supra* note 47, at 1650-51.

standard of protection rather than strengthening it as intended.⁹⁰

A. Bilateral Efforts: Mutual Recognition Agreements (MRAs) and Memoranda of Understanding (MOUs)

1.

Mutual Recognition Agreements (MRAs)

Generally, an MRA is a trade agreement under which non-tariff barriers to trade are eliminated to facilitate trade between the parties to the agreement.⁹¹ The overall goal of an MRA is to make trade easier without compromising on levels of safety. MRAs generally involve either reliance on one another's conformity assessment system or exchange of results from conformity assessments to assure that requirements of the receiving country are complied with where reliance on another's results is not practicable.⁹² An MRA is a negotiated, reciprocal agreement between two or more countries under which each recognizes the others' conformity assessment systems to be of a caliber such that some types of testing upon importation of pharmaceuticals are unnecessary.⁹³ Such agreements establish a framework of cooperation and trust between the involved regulatory bodies. Evaluation, testing or inspection decisions of a regulatory authority in the exporter's jurisdiction are accepted by the importing country, as long as they are equivalent to those which would have been made in the importing jurisdiction. The focus is thus on the capabilities and equivalency of the procedures to reach the same decisions regarding testing, evaluation, or inspection, rather than on requiring harmonization of regulatory requirements.⁹⁴ Thus, even though other countries have much less extensive

⁹⁰ See Donahue, *supra* note 23, at 365-366.

⁹¹ See Therapeutic Products, *supra* note 33.

⁹² See Horton, *supra* note 82, at 715.

⁹³ See *Accountable Governance*, *supra* note 70.

⁹⁴ See Therapeutic Products, *supra* note 33.

regulatory capacities than the United States, the U.S. may declare another country's procedures "equivalent" if the U.S. has confidence that that country's system will produce the same caliber of decision-making.⁹⁵

As opposed to the more wide-reaching ICH, MRAs are generally tailored to solving a particular problem. They are utilized most often to address situations in which a particular difference in regulatory regimes is deemed a significant barrier to trade.⁹⁶ For example, the E.U.-U.S. MRA arose in part out of the US's fear of the EU becoming a fortress from which the US would be excluded. As a side benefit, the MRA addressed increasingly unmanageable enforcement burdens as well.⁹⁷ Also, in opposition to the atmosphere of neutral scientific curiosity that generally marks the ICH, MRAs often involve negotiations in which a spirit of competitiveness prevails over cooperation.⁹⁸

It is important to emphasize that MRAs do not substitute the substantive regulations of a foreign country for that of the country into which the goods are to be imported; rather they allow foreign bodies to carry out the procedures by which adherence to domestic standards is ensured. Specifically, under an MRA, the United States would permit foreign drug regulators to inspect that country's drug manufacturers for compliance with United States' regulatory requirements, and the FDA would then treat these reports as if they came from U.S. regulators.⁹⁹ However, industry groups intend MRAs to be a step toward equivalence and standardization, as they generally necessitate some determinations of equivalency.¹⁰⁰ For example, the US-EU MRA requires that both countries adhere to equivalent manufacturing standards as a prerequisite for inclusion of products in the MRA.¹⁰¹ Even while emphasizing that the MRA did not involve harmonization of drug regulations, the FDA described harmonization as a natural outcome of an MRA.¹⁰²

⁹⁵ Although, such determinations by the U.S. raise the question as to why the U.S. requires more extensive regulation if it determines that less stringent regulations are "equivalent" in producing decisions about pharmaceutical safety.

⁹⁶ See George A. Bermann, *Regulatory Cooperation Between the European Commission and U.S. Administrative Agencies*, 9 **Admin. L.J. Am. U.** 933, 964 (1996).

⁹⁷ See *id.*

⁹⁸ See *id.* at 966.

⁹⁹ See *Accountable Governance*, *supra* note 70.

¹⁰⁰ See *id.*

¹⁰¹ See *id.*

¹⁰² See *id.*

In the United States, attempts to establish MRAs with other countries are headed by the U.S. Trade Representative, with the involvement of the FDA for agreements on pharmaceuticals.¹⁰³ Conformity assessment systems ensure that a product meets with a given standard, through means such as product testing and reporting on the results of quality tests.¹⁰⁴ Thus, the regulatory agencies are relying on their counterparts in the other countries to assess the conformity of drugs with safety and efficacy requirements.¹⁰⁵ Since each party recognizes the trials and approvals issued by conformity assessment agencies of the other party, products can be exported into the other party's market without undergoing additional testing.

The United States initialed an MRA with the EU on June 20, 1997.¹⁰⁶ The MRA entered into force on December 7, 1998 with a three year confidence-building period,¹⁰⁷ after both parties completed domestic requirements for adoption of the MRA.¹⁰⁸ The MRA is composed of a general Framework Agreement section laying out the rights and obligations of the parties, as well as sector-specific annexes, including one on inspections in pharmaceuticals.¹⁰⁹ It calls for mutual acceptance of products made at sites that have passed inspection that adhere to international pharmaceutical manufacturing standards, known as Good Manufacturing Practice (GMP), which ensure the purity and quality of the final drug product.¹¹⁰ Under the MRA, the FDA is to determine whether the regulatory systems of EU members are equivalent to that of the US, after which those nations can import pharmaceuticals into the US without submission to the FDA for further testing of products produced under GMP standards.¹¹¹ The GMP Annex of the MRA defines

¹⁰³See John Y. Chai, *Medical Device Regulation in the United States and the European Union: A Comparative Study*, 55 **Food & Drug L.J.** 57, 75 (2000).

¹⁰⁴See *Accountable Governance*, *supra* note 70.

¹⁰⁵See Chai, *supra* note 103.

¹⁰⁶See Senie and Helne, *supra* note 68, at 229. The text of the MRA can be found at <http://www.fda.gov/oia/ecmutual.htm>, visited on April 1, 2002. The EU also completed MRAs with Canada, New Zealand, and Australia at around the same time. See Senie and Helne, *supra* note 68, at 229.

¹⁰⁷See Indech, *supra* note 1, at n231.

¹⁰⁸See Senie and Helne, *supra* note 68, at 229. In the U.S., consultations with Congress and industry groups, as well as an FDA-mandated notice and comment period are required for adoption of an MRA. *See id.*

¹⁰⁹*See id.*

¹¹⁰See John R. Schmertz and Mike Meier, *European Union, Canada, and U.S. Conclude Mutual Recognition Agreements to Facilitate the Sale of Certain Products in Each Other's Markets*, **Int'l Law Update**, 87 (1997).

¹¹¹See *Accountable Governance*, *supra* note 70.

equivalence as involving systems [that] are sufficiently comparable to assure that the process of inspection and the ensuing inspection reports will provide adequate information to determine whether respective statutory and regulatory requirements of the authorities have been fulfilled;] Equivalence does not require that the respective regulatory systems have identical procedures.¹¹² Activities implicated in assessing equivalence include exchanges of information, joint training, and joint inspections between the FDA and its EU Member States' counterparts.¹¹³ Equivalence determinations by both parties are to be made after the three year transitional period, based on the evidence gathered during the transitional period.¹¹⁴ These assessments will be carried out by a Joint Sectoral Committee, chaired by a representative of each party, and the Committee will generate a list of equivalent authorities. In the pursuant operational stage, GMP inspection reports will be exchanged between equivalent authorities, which in most cases will be endorsed by the receiving party.¹¹⁵ Eliminating the need for duplicating tests, inspections, and certifications is expected to bring a cost savings of more than \$1 billion each year to United States manufacturers, which amounts to the equivalent of a two to three percent tariff reduction.¹¹⁶

The FDA requires equivalence as a prerequisite to an MRA. As such, the FDA often uses MRAs to deepen an already existing MOU relationship.¹¹⁷ MRAs generally specify the ongoing procedures by which the countries will recognize the results of tests carried out by the other party's regulatory body. An MRA sets out the requirements a regulatory agency must meet for recognition, as well as the range of products to be

¹¹²See *id.*

¹¹³See Nick Littlefield and Nicole R. Hadas, *A Survey of Developments in Food and Drug Law From July 1998 to November 1999*, 55 **Food & Drug L.J.** 35, 49 (2000).

¹¹⁴See Horton, *supra* note 82, at 727.

¹¹⁵See *id.* at 728-729. Under this procedure, the FDA still retains the possibility of rejecting such reports, although such power is intended to be used only rarely, and thus the ultimate say on compliance. See *id.*

¹¹⁶See Charles Owen Verrill, Jr., Peter S. Jordan, and Timothy C. Brightbill, *International Legal Developments in Review: 1997 Business Transactions, Disputes, and Regulation*, 32 **Int'l Law.** 319, 326. (1998). This figure includes cost savings accrued from all products covered by the MRA, not just pharmaceuticals. See *id.*

¹¹⁷See Horton, *supra* note 82, at 720.

covered under the agreement.¹¹⁸ Equal access to markets is to be afforded to all products covered by the MRA. If barriers to such access arise, the parties must consult on how best to resolve the issue.¹¹⁹ In the absence of resolution, the agreement may be dissolved by the complaining party after a certain amount of time.

Given the highly technical nature of MRAs and the scope and nature of the negotiations they thereby require, such agreements are not optimal in all situations.¹²⁰ In fact, MRAs are only practical and effective when a trading relationship is one in which the nations have regulatory structures that are similar in scope and structure, the countries have a significant amount of trade in the particular industry to be covered, and the standards differential has become a contentious trade issue between the nations.¹²¹ For an MRA to be appropriate, the trading partners to be covered should both have regulatory systems that are similar in scope and structure and should conduct a large amount of trade in the industry to be covered.¹²² Furthermore, due to the scope and nature of negotiations involved in concluding an MRA, the standards to be regulated should have become contentious issues.¹²³

Even if these factors are present, an MRA may still encounter problems in implementation, such as those already experienced with the EU-US MRA. The transitional period of the MRA had been marked by ambivalence. Because of the voluntary nature of the MRA, manufacturers can opt to use conventional FDA or EU-equivalent inspections.¹²⁴ The EU did not supply the US with a list of conformity assessment bodies (CABs) until four months after the US submitted its own list of nominees. Additionally, CABs charge fees based on the number of manufacturers it serves, and certification of the EU CABs will cost the FDA about \$18 million in training.¹²⁵

¹¹⁸See Chai, *supra* note 103, at 76.

¹¹⁹See *id.*

¹²⁰See Senie and Helne, *supra* note 68, at 234 (1998).

¹²¹See *id.* at 234-235.

¹²²See *id.*

¹²³See *id.* at 235.

¹²⁴See Littlefield and Hadas, *supra* note 113.

¹²⁵See *id.*

2.

Memoranda of Understanding (MOUs)¹²⁶

Memoranda of Understanding (MOUs) are another tool used in standardization of regulatory regimes. MOUs are sometimes referred to as Notes Verbale or Arrangements. MOUs promote standardization of laws, regulations, and enforcement actions.¹²⁷ Like the other standardization tools, MOUs are intended to ensure the safety and efficacy of pharmaceuticals, to enhance efficiency of resource utilization, and to further communication between regulatory bodies on covered drugs.¹²⁸

MOUs can be structured in various ways, depending on the nature of the parties' systems and relationship.¹²⁹

Not all MOUs are reciprocal and therefore do not always offer the same benefits to each side.¹³⁰

One type of MOU that is most useful with countries having the same or similar systems offering approximately the same level of protection is a reciprocal agreement setting up the mutual assessment of a foreign regulatory system or measure's comparability.¹³¹ These MOUs may be very similar to MRAs or equivalence determinations, with the scope of activities covered ranging from mutual acceptance of data and inspection results to acceptance of the regulatory system such that the tests and inspections of imports may be reduced.¹³² Several longstanding MOUs, for example those between the U.S. and Canada, and the U.S.

¹²⁶Because MOUs can take a variety of forms, it is often unclear what the real differences are between MOUs and MRAs, and this confusion is not resolved in the literature on standardization agreements. For example, no article spelled out the different areas in which an MRA would be used over an MOU and visa versa.

¹²⁷See Department of Health and Human Services, *supra* note 85, at 31485.

¹²⁸See Chai, *supra* note 103, at 77.

¹²⁹See Department of Health and Human Services, *supra* note 85.

¹³⁰See Horton, *supra* note 82, at 720.

¹³¹See Department of Health and Human Services, *supra* note 85.

¹³²See *id.*

and Sweden, have mutual recognition components, added after the FDA has determined that that the other country's regulatory system is of a caliber that the FDA can safely reduce inspections of products from that country.¹³³

MOUs may also cover certification criteria for regulated products.¹³⁴ In the past, these agreements have been limited to products with inherent or consistent safety issues.¹³⁵ More recently, they have been extended to products with a good compliance history.¹³⁶ This type of MOU can be used to direct the exporting country as to what controls to use to ensure reliable and valid certification, with the goal of reducing the need for inspections and samplings upon import of the products.¹³⁷

Yet another type of MOU establishes formal means of communication between signatories. Enhanced communication facilitates the exchange of technical, regulatory, and scientific information, improving decision-making by both parties and limiting resources needed for monitoring.¹³⁸ Employees may also be exchanged, as well as information. These MOUs are generally limited to a specific time period.¹³⁹

There are several other varieties of MOUs. A cooperation MOU fosters cooperation and information-sharing.¹⁴⁰ A compliance MOU requires compliance of the exporting country with the standards of the importing company. An equivalents MOU finds the regulatory system of another country equal to the FDA's.¹⁴¹

¹³³ See Horton, *supra* note 82, at 720.

¹³⁴ See Department of Health and Human Services, *supra* note 85.

¹³⁵ See *id.*

¹³⁶ See *id.*

¹³⁷ See *id.*

¹³⁸ See *id.*

¹³⁹ See Therapeutic Products, *supra* note 33.

¹⁴⁰ An example of such an MOU is an agreement signed by FDA and its counterparts in Canada and Mexico (Memorandum of Cooperation in FDA International Cooperative Agreements Manual). See Horton, *supra* note 82, at 719.

¹⁴¹ See Horton, *supra* note 82, at 719-720.

The FDA has turned to MOUs in the face of increases in imports that need to be examined by the FDA. Import shipments have increased from 500,000 in 1970 to 3,700,000 in 1996. The FDA negotiated MOUs to have other countries take on the burden of ensuring that FDA requirements were met before the products were sent to the U.S. As of 1996, the FDA had negotiated almost fifty MOUs.¹⁴²

In 1995, the FDA published a new compliance policy guide, “International Memoranda of Understanding,” setting forth guidelines for initiating, developing, and monitoring MOUs between the FDA and with other countries.¹⁴³ These guidelines were developed at the recommendation of the FDA’s International Harmonization Task Force, to explain the FDA’s aims in forging MOUs and to promote uniformity in the establishment of MOUs.¹⁴⁴ The guide stresses the need to maintain flexibility in negotiating MOUs to accommodate different approaches to regulation.¹⁴⁵

The FDA pursues MOUs with foreign governments or organizations when such agreements will advance the state of domestic public health by improving FDA’s capacity to ensure the safety, quality, and effectiveness of products, allowing the FDA to capitalize on its resources most effectively without compromising public safety, and enhancing communications with foreign regulators.¹⁴⁶ Particularly, the following factors are considered in deciding whether to initiate MOU talks: health benefits, including risk reduction, of products and programs; to what extent a product is imported into the United States; the degree to which a proposed agreement will remedy past compliance issues; the extent to which the costs of the program will outweigh

¹⁴²See Sharon Smith Holston, An Overview of International Cooperation, 52 **Food & Drug L.J.** 197, 198 (1997).

¹⁴³See Department of Health and Human Services, *supra* note 85.

¹⁴⁴See *id.*

¹⁴⁵See *id.*

¹⁴⁶See *id.*

the benefits;¹⁴⁷ the resulting reduction in industry's regulatory burden; and the broader international policy objectives of the United States.¹⁴⁸

FDA negotiates MOUs pursuant to the Department of State's Circular 175 procedures governing clearance of Agency agreements with foreign powers.¹⁴⁹ Before making equivalence determinations regarding procedures and enforcement mechanisms of other parties, the FDA checks whether such procedures are in fact equivalent in the level of safety and efficacy they provide.¹⁵⁰ On-site visits, among other techniques, are used to ascertain whether the authorities, product standards, capabilities, and infrastructure of the foreign country make it feasible for that country to meet the terms of an MOU.¹⁵¹ An MOU generally lasts for 5 years, during which it is reviewed at least once to determine whether modifications are needed and if it should be continued or cancelled.¹⁵²

The FDA uses a three-phase process in developing an MOU with a foreign country, involving coordination between the sponsoring center or office, the Office of Regulatory Affairs (ORA), and the International Affairs Staff/Office of Health Affairs (IAS/OHA), and the Office of Policy (OP).¹⁵³ First, the feasibility of such an MOU is evaluated. The sponsoring center or office explains in writing to the ORA how the proposed MOU would further FDA goals. The FDA determines whether the other party will be capable of carrying out the proposed MOU, potentially through an exchange of information on laws, standards, and inspection and sampling procedures and through on-site visits to various facilities. If the FDA decides that the other

¹⁴⁷The goal is provide the greatest benefit in relation to the resources required to administer a program. For example, the costs of developing, implementing, and monitoring an agreement should be measured against the alternative, like the costs of higher sampling levels to obtain the same degree of confidence in rates of compliance in the absence of an agreement. *See id.* at 31486.

¹⁴⁸*See* Department of Health and Human Services, *supra* note 85, at 31486.

¹⁴⁹*See id.* at 31485.

¹⁵⁰*See id.*

¹⁵¹*See id.* at 31486.

¹⁵²*See id.*

¹⁵³*See id.*

party does not have an adequate infrastructure to successfully participate in the MOU, a letter to that effect, approved by the OP and IAS/OHA, is sent to that party, and talks are suspended until the specified concerns are addressed.¹⁵⁴

Second, effectiveness must be determined. Sometimes an informal confidence-building trial period is conducted under a draft MOU. The protocol detailed in the draft may include: a program description, information about relevant government and private organizations' roles and capabilities, possible certification issuance and use, procedures relating to audit time frames and metrics, and necessary training and information. Regardless of the conduct of a trial, the FDA can use inspections, alone or with the other party, and analysis of imported products to assess program effectiveness.¹⁵⁵

In the third stage, the substance of the MOU is finalized. Rulemaking is conducted if necessary. The MOU is then ready for official clearance. Procedures by which to audit the MOU are developed by the sponsoring center or office and are disseminated to field offices by the ORA.¹⁵⁶

The FDA MOU with Russia, announced by the FDA on February 14, 1994, effectively makes the FDA the regulatory body regarding pharmaceuticals for Russia.¹⁵⁷ Under the MOU, the Russian Ministry of Health is obligated to grant permission for the free marketing of U.S. pharmaceuticals within ninety days of the provision of the applicant company's financial information, an FDA approval letter and package insert for the product, a statement showing compliance with FDA GMP, and a copy of the FDA manufacturing facility inspection report.¹⁵⁸ No longer is further review or testing necessary and no translation of the underlying

¹⁵⁴See Department of Health and Human Services, *supra* note 85, at 31486.

¹⁵⁵See *id.*

¹⁵⁶See *id.*

¹⁵⁷See Walser, *supra* note 47, at 1650-1651. Controlled substances or highly addictive products must still be approved by the Russian Federation's State Committee on Controlled Substances. Additionally vaccines are subject to extra regulations. See *id.*

¹⁵⁸See *id.* at 1653-1654.

data into Russian is required.¹⁵⁹ This dramatically speeds up the entry of U.S. drugs into the Russian market. Prior to this agreement, U.S. pharmaceutical companies often had to repeat animal and human clinical trials, have all submitted papers, which often comprised over a thousand pages, translated into Russian, and wait undefined periods for approval decisions to be made.¹⁶⁰ This would allow the United States a comparative advantage in increasing its market share in the Russian pharmaceutical market.¹⁶¹ Furthermore, the formal recognition of the worldwide esteem in which the FDA was held, was a boost to FDA self-esteem and validation of the high-standards it claimed to uphold.¹⁶² Humanitarian concerns for getting treatments to those that needed them in Russia were also cited.¹⁶³

From the Russian viewpoint, the pact provided Russians with much needed pharmaceuticals that were in short supply in Russia.¹⁶⁴ The Russians also hoped that U.S. companies would hire Russian clinicians to conduct lower cost drug trials in new facilities in Russia and that such a pact would promote joint ventures to sell Russian products.¹⁶⁵ Russia's decision to essentially substitute the FDA for a domestic regulatory agency can be viewed as a response to a weak domestic pharmaceutical industry,¹⁶⁶ the quality problems suffered by domestic drug producers, and the lack of resistance to such action from any internal community.¹⁶⁷ Rather than sink limited resources into an expensive revamping of its own unsuccessful regulatory agency, the Russian ministry of health ceded authority to the FDA. Furthermore, the MOU frees up limited Russian resources to concentrate on other more problematic goods entering the country from other parts of the

¹⁵⁹See *id.* at 1654.

¹⁶⁰See *id.* at 1651.

¹⁶¹At the time, the United States accounted for only \$7 million of the \$350 million of drugs Russia imported. See *id.* at 1653.

¹⁶²See Walser, *supra* note 47, at 1652.

¹⁶³See *id.* at 1653.

¹⁶⁴See *id.* at 1651.

¹⁶⁵See *id.* at 1651-52.

¹⁶⁶By 1995, foreign firms selling drugs already approved in their domestic markets made up about eighty-five percent of Russian drug sales. See *id.* at 1652.

¹⁶⁷See Walser, *supra* note 47, at 1652.

world.¹⁶⁸

B. Multilateral Efforts: The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)

1.

Goals of the ICH

The ICH was conceived at a conference between the regulatory officials of the EU, Japan, and the U.S. and the International Federation of Pharmaceutical Manufacturers Associations (IFPMA) in 1989¹⁶⁹ and initiated in 1990 to achieve convergence of the pharmaceutical regulatory regimes of the U.S., the EU and Japan.¹⁷⁰ The project brings together representatives of the regulatory bodies of each of the three countries, as well as industry experts from these countries, to discuss scientific and technical issues regarding drug registration.¹⁷¹ Three government bodies, the European Commission; Japanese Ministry of Health and Welfare; and U.S. Center for Drug and Biologics Evaluation and Research (an office of the FDA), and three pharmaceutical industry trade groups, the European Federation of Pharmaceutical Industries Association; Japanese Pharmaceutical Manufacturers Association; and Pharmaceutical Research and Manufacturers of America comprise the ICH.¹⁷² The ICH is different from other moves toward standardization, such as those promoted by the WTO, as it has a recognized status and is supported by industry groups and regulatory

¹⁶⁸ See Horton, *supra* note 82, at 720.

¹⁶⁹ See Dan 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, 185 (1996).

¹⁷⁰ See Booth, *supra* note 8, at 203. As of 1994, these countries accounted for 75 percent of the world's pharmaceutical market and produce ninety percent of all pharmaceutical research. See Kanusky, *supra* note 19, at 767 (1994).

¹⁷¹ See *Welcome to the Official Web Site for ICH*, at <http://www.ifpma.org/ich1.html>, visited on January 27, 2002.

¹⁷² See *Accountable Governance*, *supra* note 70. No consumer groups are included in the ICH, a critique I will expand on later in this paper.

bodies.¹⁷³

The ICH is programmatic in that it contemplates a wide-ranging plan to address all areas of pharmaceutical regulation in an institutionalized solution.¹⁷⁴ The program is based on the notion that the core of drug development is asking key questions and trying to answer them with studies that demonstrate to regulatory authorities with a given level of confidence the safety, efficacy, and quality of the resulting products. This principle, that drug development can be broken down into scientific principles and technical requirements to which best scientific practice can be applied, suggests that the development of international standards for pharmaceuticals is the logical outcome of adherence to such a principle.¹⁷⁵ The goals of ICH, set out in a statement by the ICH Steering Committee, are threefold.¹⁷⁶ First, standardization is sought as a means to avoid wasteful duplication in developing new drugs, without compromising levels of safety and efficacy,¹⁷⁷ or to ensure that “good quality, safe and effective medicines are developed in the most expeditious and cost effective manner.”¹⁷⁸ Specifically, standardization would reduce the need for animal, human, and material, including monetary, resources.¹⁷⁹ Second, ICH is intended to reduce the time to market of new drugs. Third, ICH will maintain the levels of safety and efficacy currently in place. ICH activities have also been touted as means to reduce the spread of disease, both within and between countries, and to improve information exchange between countries on health issues.¹⁸⁰ In enacting these measures, the best interests of the patients,

¹⁷³See Kanusky, *supra* note 19, at 691.

¹⁷⁴See Bermann, *supra* note 96, at 961.

¹⁷⁵See Caroline Nutley, *supra* note 29, at 2.

¹⁷⁶In the Statement by the ICH Steering Committee “[t]he Parties cosponsoring th[e] Conference, represented at the 2nd Steering Committee Meeting in Tokyo, 23-24 October 1990 re-affirmed their commitment to increased international harmonisation, aimed at ensuring that good quality, safe and effective medicines are developed and registered in the most efficient and cost-effective manner. These activities are pursued in the interest of the consumer and public health, to prevent unnecessary duplication of clinical trials in humans and to minimise the use of animal testing without compromising the regulatory obligations of safety and effectiveness.” *Statement By the ICH Steering Committee Tokyo, October 1990*, at <http://www.ifpma.org/ich8.html>, visited March 10, 2002.

¹⁷⁷See Miller, *supra* note 11, at 228.

¹⁷⁸See *A Brief History of ICH*, at www.ifpma.org/ich8.html visited July 29, 1999, cited in Indech, *supra* note 1, at 367.

¹⁷⁹See *Welcome to the Official Web Site for ICH*, at <http://www.ifpma.org/ich1.html>, visited on March 31, 2002.

¹⁸⁰See Miller, *supra* note 11, at 228.

public health, and the consumer are to be paramount.¹⁸¹

2. History of the ICH

ICH conferences have been held in Brussels, Belgium (ICH1) (1991), Orlando, Florida (ICH2) (1993), Yokohama, Japan (ICH3) (1995), Brussels (ICH4) (1997),¹⁸² San Diego, California (ICH5) (2000),¹⁸³ and ICH6 is planned for 2003.¹⁸⁴ ICH1 produced a procedure by which to promulgate harmonization guidelines.¹⁸⁵ A Steering Committee composed of two representatives from each region plus two non-voting representatives of the International Federation of Pharmaceutical Manufacturers Associations (IFPMA) was constituted to direct and oversee all ICH activities, which in turn established a system of Expert Working Groups (EWGs), joint regulatory/industry bodies, to establish priorities and draft guidelines.¹⁸⁶ The first phase of ICH, which ended with ICH4 in Brussels, focused on decreasing duplication in the development process by standardizing technical guidelines. The second phase focuses on consolidating, updating, and promoting the acceptance of the Guidelines that grew out of the first phase,¹⁸⁷ as well as preventing future problems through early collaboration on newly emerging issues.¹⁸⁸

¹⁸¹See Indech, *supra* note 1, at 368.

¹⁸²See Booth, *supra* note 8, at 203.

¹⁸³See ICH Global Cooperation Group, *ICH Information Brochure*, 5, May 2001, at <http://www.ifpma.org/ichGCG.html>, visited March 31, 2002.

¹⁸⁴See *JPMA to prepare for ICH6 in Japan in 2003*, 5/22/01 Chemical Bus. NewsBase 6, 2001 WL 21408934.

¹⁸⁵See Buono, *supra* note 9, at 149.

¹⁸⁶See *id.* at 149-150.

¹⁸⁷See Holston, *supra* note 142, at 199-200.

¹⁸⁸See ICH Global Cooperation Group, *ICH Information Brochure*, 21, May 2001, at <http://www.ifpma.org/ichGCG.html>, visited March 31, 2002.

3.

Organizing Documents of the ICH

The ICH sets out its mission in the “Terms of Reference” under which it operates.¹⁸⁹ Apart from ascertaining where increased standardization could produce a more economical use of resources while maintaining quality and safety levels, the ICH serves as a forum for regulatory agencies to converse constructively with industry groups and to recommend practical steps toward standardization of the registration process.¹⁹⁰ Rather than ostensibly seeking harmonization of the regulations governing the approval process or a common application process, the ICH aims to standardize the drug testing guidelines such that data produced therein would be acceptable across countries.¹⁹¹ Achievement of ICH’s aims would obliterate the need for drug producers to duplicate trials, while still requiring that each country’s application process be followed.¹⁹² Inevitably, a quite similar regulatory process will result if ICH is successful.

4.

Structure of the ICH

The current ICH structure includes a Secretariat and Coordinators, in addition to the Steering Committee and the EWGs.¹⁹³ The Steering Committee currently has a representative from each of three observers, the World Health Organization (WHO), Canada (represented by the Health Canada Drugs Directorate), and

¹⁸⁹ See Global Cooperation Group, *Questions and Answers about ICH*, 6, at <http://www.ifpma.org/pdfifpma/GCGQ&A.pdf>, visited on January 27, 2002.

¹⁹⁰ See Buono, *supra* note 9, at 148-149.

¹⁹¹ See Booth, *supra* note 8, at 204.

¹⁹² See *id.*

¹⁹³ See Global Cooperation Group, *Questions and Answers about ICH*, 5, at <http://www.ifpma.org/pdfifpma/GCGQ&A.pdf>, visited on January 27, 2002.

the European Free Trade Area ((EFTA) represented by Switzerland), in addition to the original members to provide input from non-represented states.¹⁹⁴ The Steering Committee meets at least twice a year, rotating locations among member regions. At these meetings, the Committee considers new topics for harmonization, hears status reports on works in progress, and discusses maintenance of existing guidelines.¹⁹⁵ Representatives from the generics industry, the over-the-counter (OTC) industry, and pharmacopoeial authorities have been invited to some of the EWGs in recognition of their interest in the outcome of the ICH.¹⁹⁶ In March 1999, a subcommittee of the Steering Committee, the ICH Global Cooperation Group (GCG) was formed to provide information on ICH, ICH activities, and ICH guidelines to any country's regulatory authority or any pharmaceutical company that requests the information. The subcommittee is constituted of one representative of each of the six parties on the Steering Committee, the ICH Secretariat at IFPMA, and observers from the WHO and Canada.¹⁹⁷ The Secretariat, provided by the IFPMA and acting from the IFPMA offices in Geneva, supports the Steering Committee's activities, with help from a coordinator from each party. The Secretariat is funded by conference proceeds and industry contributions, while each member funds its own participation in ICH activities, including travel expenses, special investigations, and experiments. Five major conferences have been held apart from Steering Committee meetings, with the aim of providing updates on ICH activities and assessing public opinion.¹⁹⁸

¹⁹⁴See *id.* at 8.

¹⁹⁵See *id.* at 5.

¹⁹⁶See Caroline Nutley, *supra* note 29, at 2.

¹⁹⁷See *ICH Global Cooperation Group*, at <http://www.ifpma.org/ichGCG.html>, visited January 27, 2002.

¹⁹⁸See Global Cooperation Group, *supra* note 183.

5. ICH Procedure

Topics for standardization are proposed by a party in a concept paper, which details the need for harmonization and the proposed task and timetable of an EWG. If the topic is accepted by the Steering Committee, an EWG is comprised to develop harmonization guidelines.¹⁹⁹

At ICH conferences the parties engage in regulatory negotiation, also known as negotiated rulemaking, in which parties aim to develop regulation guidelines on which all participants can agree.²⁰⁰ Cooperation is intended to be placed above competition, as the participants engage in a neutral scientific inquiry.²⁰¹ The notice and comment period about the resulting compromise proposal should therefore be streamlined and parties are less likely to challenge such a proposal in court once it has been accepted.²⁰²

The ICH process for generating standardizing proposals can be divided into five steps which are carried out primarily by working groups between conferences.²⁰³ First, in the consensus-building stage, the Expert Working Groups (EWGs) select and prioritize topics for standardization.²⁰⁴ The EWGs forward a draft guideline, policy statement, or similar document to the Steering Committee.²⁰⁵ Second, regulatory action starts when the Steering Committee determines based on the EWG report that there is enough consensus to proceed and the members from each country regulatory group assent.²⁰⁶ At this point, proposed ICH guidelines are published for comment on the ICH and member parties' web sites.²⁰⁷ Third, during the regulatory consultation stage, each member regulatory agency has six months to exhaust its own consultation

¹⁹⁹See *id.*

²⁰⁰See Booth, *supra* note 8, at 231.

²⁰¹See Bermann, *supra* note 96, at 966.

²⁰²See Booth, *supra* note 8, at 231.

²⁰³See Bermann, *supra* note 96, at 963.

²⁰⁴See Miller, *supra* note 11, at 229.

²⁰⁵See Booth, *supra* note 8, at 205.

²⁰⁶See ICH Global Cooperation Group, *ICH Information Brochure*, *supra* note 183, at 17.

²⁰⁷See ICH Global Cooperation Group, *Questions and Answers about ICH*, *supra* note 189, at 8.

procedure.²⁰⁸ Such consultation processes usually involve soliciting comments from citizens, academics, and industry groups, among others.²⁰⁹ In the United States, proposed guidelines are published for comment in the Federal Register.²¹⁰ Comments from each agency are incorporated into the draft and passed to the EWGs for approval before submission to the Steering Committee.²¹¹ At this stage, industry associations and regulatory authorities in non-ICH regions have a chance to comment on the draft documents which are distributed using IFPMA and WHO contact lists.²¹² A Regulatory Rapporteur is designated to meld the drafts together and have the regulatory body representatives sign-off on the final document.²¹³ Fourth, the Steering Committee adopts and recommends the final version to all parties for their adoption.²¹⁴ Fifth, the parties incorporate the final guidelines into their domestic pharmaceutical regulations.²¹⁵

A guideline produced by the ICH is not binding on its members, as it lacks the force of a treaty or an international accord. Rather, it represents a firm political commitment on the part of the concerned governments.²¹⁶ For implementation of its guidelines, the ICH relies on their integration into domestic law by the regulatory agencies of each country.

²⁰⁸See Booth, *supra* note 8, at 205.

²⁰⁹See Indech, *supra* note 1, at 368.

²¹⁰See Booth, *supra* note 8, at 205.

²¹¹See *id.*

²¹²See ICH Global Cooperation Group, *ICH Information Brochure*, *supra* note 183, at 17.

²¹³See *id.*

²¹⁴See Miller, *supra* note 11, at 229.

²¹⁵See *id.*

²¹⁶See *International Agreements: EC, U.S. and Japan Sign Commitment to Standardize Pharmaceutical Tests*, 8 **Int'l Trade Reporter** 1702, 1702 (1991). However, for such commitments to come to fruition, each country must integrate the ICH guidelines into domestic law.

6. Progress of the ICH

Topics to be harmonized are classified as within the category of Safety, Quality, or Efficacy, the three criteria on which approval of new drugs is based, or Multidisciplinary.²¹⁷ “Efficacy” includes clinical testing programs and safety monitoring, “Quality” includes pharmaceutical development and specifications, “Safety” includes pre-clinical toxicity and related tests, and “Multidisciplinary includes topics effecting more than one area, such as regulatory communications, including electronic communication, medical terminology, timing of toxicity studies in relation to clinical studies, and the Common Technical Document (CTD)). Eleven guidelines have been published regarding Efficacy, with three more in final stages of development. Efficacy guidelines have the potential to be the guidelines with the most impact, since clinical trials are the most resource intensive part of drug development. For example, with the implementation of “Ethnic Factors in the Acceptability of Foreign Clinical Data” (E5) after its publication in February 1998, drug companies were able to avoid repeated trials to account for ethnic differences across countries. Pfizer benefited from this guideline in its introduction of Viagra in Japan.²¹⁸ However, the impact has been undermined by the U.S. and Japan’s reluctance to accept data from other countries, with Japan in particular requiring extensive use of bridging studies that are supposed to only be conducted in rare cases under E5.²¹⁹ E5 has already been adopted by some non-ICH countries, such as Taiwan and South Korea.²²⁰ The “Good Clinical Practice: Consolidated Guideline” (E6), which underlies E5 by requiring adherence to the same rigorous clinical standards across countries, has already effected regulatory change in member countries. “General Considerations for Clinical Trials” (E8), finished in July 1997, details internationally accepted principles of trial design, facilitating the

²¹⁷See Caroline Nutley, *supra* note 29, at 2-3. See *id.* for a list of guidelines under consideration in each category, as well as the texts and current stage of consideration of such guidelines.

²¹⁸See Caroline Nutley, *supra* note 29, at 3.

²¹⁹See *Japan, U.S., but Not E.U., Are Slow to Accept Others’ Trial Data*, 7/16/01 Eur. Drug & Device Rep. (Pg. Unavail. Online) 2001 WL 15576169 Vol. 11, No. 14. Under the ICH guide, extrapolation of data from one region to other regions is contemplated with limited use of bridging studies, trials to test whether ethnic differences effect differential impacts of drugs. See *id.*

²²⁰See *id.*

acceptance of data across countries.²²¹ According to a 1997 ICH Utilization Survey, based on only seven available Efficacy guidelines, industry use of the guidelines in the EU 62%, Japan had 77% utilization, and the US had 85% utilization, with industry reporting a positive impact on drug development programs.²²² Specifically, industry responses noted that the guidelines facilitated intra-company globalization and some, although not total, reduction of duplicate research.²²³

The fourteen finalized Quality guidelines focus on stability, specifications, and analytical methods evaluation. Recommendations on stability data and impurities, two key areas of bulk drug and drug product quality, have reduced the duplication of tests. For example, specifying a particular temperature at which to run stability tests, rather than just conducting them at room temperature, eliminated the need for additional tests for each climate.²²⁴ The 1997 ICH Utilization Survey, based on the 11 guidelines in this area then completed, reported 77% average utilization and a reduction of duplication in research.²²⁵ The reported regulatory issues were then addressed in revisions of the relevant guidelines.

Safety guidelines, covering all the major types of pre-clinical toxicity testing and focusing on standardizing study length, content, species requirements, dose selection and

exposure levels to improve the risk/benefit assessment, have increased the acceptability of the studies in this ethically sensitive area. Standard batteries of tests have been developed for each type of toxicity study. Utilization rates as of the 1997 survey, when seven guidelines had been implemented was 80.5% over the three regions, with the EU reporting 77% utilization, and with Japan and the US both reporting 82% utilization.²²⁶

²²¹ See Caroline Nutley, *supra* note 29, at 4.

²²² See *id.* at 2.

²²³ See *id.* at 5.

²²⁴ See *id.*

²²⁵ See *id.* at 6.

²²⁶ See *id.* at 7.

The Common Technical Document (CTD) and the Medical Dictionary for Regulatory Activities Terminology (MedDRA), a standardized terminology for the reporting of Adverse Drug Reactions, are the most important and most ambitious Multidisciplinary guidelines. The CTD is a product of three EWGs promulgating a single format for the technical section of a new drug dossier.²²⁷ The CTD, which creates a standard format and content for new product applications, is the logical outgrowth of agreement on technical guidelines for generating the reporting data.²²⁸ Currently, reformatting the submissions from U.S. to EU standards takes two to six months, according to one study.²²⁹ This common document will dramatically reduce number of man hours needed to take data and present it according to various countries' requirements. The CTD is also expected to lead to reductions in review times by regulatory agencies and hence faster times to market. An e-CTD will further speed submissions.²³⁰

Several guidelines have been incorporated into domestic regulations of the member states, and the latest survey data shows that the guidelines have reduced research duplication.²³¹ These guidelines cover: 1) reproductive toxicity in animals, 2) clinical studies in which the elderly are subjects, 3) testing the stability of new active substances, 4) dose response information in support of drug registration,²³² and 5) good clinical practices, including preparing, monitoring, reporting, and archiving clinical trials.²³³ As of January 2000, 37 guidelines had been produced and are in the process of being implemented.²³⁴ The ICH is continuing to maintain current guidelines, as well as develop new ones. The Common Technical Document, along with its electronic version, is expected to allow multiple submissions to be replaced by one technical dossier for

²²⁷See *id.* at 8.

²²⁸See ICH Global Cooperation Group, *ICH Information Brochure*, *supra* note 183, at 5.

²²⁹See Kim Coghill, *New Application Procedures Streamline International Filings*, 9/4/01 *Bioworld Today* (Pg. Unavail. Online)2001 WL 7295624. Volume 12; Issue 171.

²³⁰See Caroline Nutley, *supra* note 29, at 8.

²³¹See *id.* at 2.

²³²See Bermann, *supra* note 96, at 964.

²³³See Janet Woodcock, *An FDA Perspective on the Drug Development Process*, 52 **Food & Drug L.J.** 145, 148 n5 (1997).

²³⁴See Caroline Nutley, *supra* note 29, at 2.

all three regions, encouraging simultaneous submission, approval and launch of new drugs. The ICH is disseminating guidelines via its web site as well as the sites of members for use by other countries too.²³⁵

III. CRITIQUE OF THE INTERNATIONAL STANDARDIZATION EFFORTS TO DATE

International standardization efforts have been criticized in several respects. At the most general level, the feasibility and desirability of standardization as an end goal has been attacked. More specifically, the tools of standardization, multilateral and bilateral, have been denigrated. Some criticisms of the tools of standardization echo the problems cited with the overall standardization process. However, some problems are specific to the ICH and MRA processes as vehicles for standardization.²³⁶ I address both levels of criticism in turn.

A.

Critique of Standardization as an End Goal

²³⁵*See id.* at 1.

²³⁶Criticism of particular tools of standardization focus on the ICH and MRAs. MOUs, perhaps because they are more limited in scope, have not been specifically denigrated as a tool of standardization in the literature.

The most fundamental critique of the standardization movement attacks the idea that standardization is the desired outcome. Opponents of standardization argue that: 1) standardization is unattainable in a world with cultural diversity; 2) standardization will only bring about a reduction in standard stringency; and 3) standardization reduces government accountability to citizens.

First, critics contend that standardization is predicated on the notion that there is an attainable universal standard. However, this may not be the case in the face of cultural and geographic diversity, giving rise to different levels of tolerable risk. For example, standard-setting takes into account objective variables, such as use of a particular product, which vary by place and culture. Therefore, in a culture in which it is the norm to take aspirin every day, the risk presented by the adverse effects of aspirin will be much different than in a culture in which taking aspirin is shunned.²³⁷

Second, there is a fear that standardization will reduce international regulation to the level of the least restrictive country. For example, the WTO and NAFTA instruct countries to use risk assessment, a process by which a level of risk deemed tolerable is chosen, in setting standards. However, the United States often chooses instead to base many regulations regarding pharmaceuticals on a policy of zero tolerance of a risk, forbidding public exposure to a risk completely. A policy of zero tolerance is safer for consumers, but problematic under NAFTA and the WTO.²³⁸ Therefore, the goal of standardization as a whole has been criticized as undermining the safety of United States' citizens.

International standards thus serve as a ceiling, rather than a floor; while provisions exist to challenge stricter

²³⁷See *Accountable Governance*, *supra* note 70.

²³⁸See *id.*

standards, no such provisions exists to contravene those who fall below international standards. Under these international regimes, members who deviate from international standards have the burden of proof to defend stricter standards from charges of interfering with trade. Stricter domestic standards must pass a range of tests to avoid being classified as trade barriers. The incentive under these regimes is to avoid setting safety standards in excess of international standards, even if stricter standards would save lives. Fear of trade sanctions that would interfere with lucrative international trade under the WTO and NAFTA thus impede the development of novel solutions to public health issues.²³⁹

Third, the development of global standards reduces the accountability of individual governments to their citizens. Decision-making is removed from more accountable state governments to international bodies largely inaccessible to citizens. These bodies determine the risk level that citizens are to live with in the absence of significant input from those affected by the standards. Due to the inaccessibility of these agencies to citizens, industry is able to exert a disproportionate influence on standard setting.²⁴⁰

B.

Critique of the Various Tools of Standardization

1.

Criticism of MRAs as a Tool for Harmonization

²³⁹ *See id*

²⁴⁰ *See id.*

MRAs have been criticized by business and consumers alike. Businesses are concerned that MRAs will not properly protect proprietary information of pharmaceutical companies, and that such business secrets will be disclosed to competitors through agreements dictating data-sharing between governments. For example, the 1997 US-EU MRA prescribes that the FDA has the discretion to claim confidential status for certain data that it submits to foreign governments for approval under the MRA. Yet, it is within the FDA's discretion to choose which data to mark as private. There is no effective remedy for halting such disclosure, as once the information has been let out any compensation is likely to prove inadequate.²⁴¹

Consumers worry about the extent to which MRAs will lack consumer input. The equivalence determinations made as part of MRAs will have a great effect on which drugs are allowed into a market. Consumers often have little impact on which regulations are declared equivalent. Few regulatory bodies solicit consumer feedback in making equivalence decisions. The FDA, for example, does not request consumer comments and makes equivalence determinations behind closed doors, in marked contrast to their policy of early notice and comment with regard to food product equivalence determinations. Consumers also worry that they will be denied access to the documents upon which equivalence assessments are made until after equivalence is granted; if it is denied, all documents will be sealed. Availability of documents currently accessible by the public might also be compromised under MRAs as not all foreign countries have Freedom of Information acts or require recall information to be published as does the United States.²⁴² When foreign inspectors take on regulatory duties on behalf of the U.S. under MRAs, consumers worry that they will not be given access to the resulting documents.

More basically, consumers are worried that safety standards will not be upheld given the existence of MRAs.

To prevent firms from seeking approval in countries with the least restrictions and then getting recognition of

²⁴¹ See James T. O'Reilly, *Implications of International Drug Approval Systems on Confidentiality of Business Secrets in the U.S. Pharmaceutical Industry*, 53 **Food & Drug L.J.** 123, 125 (1998).

²⁴² See *Accountable Governance*, *supra* note 70.

the decision in other nations, MRAs should only be concluded if regulatory systems are really equivalent.²⁴³

2.

Problems with the ICH as a Means of Standardization

There are many criticisms of the ICH process. Specifically the goals of the ICH, the inclusiveness of the process, the scope of the issues to be standardized, and the pace of harmonization have all come under attack.

The goals of the ICH and the metric used to assess progress is not clear. While success of the ICH seems to be measured in decreased costs to the consumers and/or manufacturers, it is unclear that decreased costs will be the result of standardization. If the United States succeeds in setting the safety level for pharmaceuticals, countries worldwide will need to impose stricter regulations on drugs produced domestically to bring their standards in line. These additional requirements will necessitate higher costs, as is evidenced by the increased costs in the United States incident to each new FDA regulation.²⁴⁴

Likewise, a major goal of the ICH is to reduce time to market for drugs entering a new market. Standardizing regulations would not necessarily accomplish this goal.²⁴⁵ The ICH is not intended to create a common approval application. Even with the implementation of the Common Technical Document (CTD), only the

²⁴³ See Dominguez-Urban, *supra* note 16, at 262-263.

²⁴⁴ See Kidd, *supra* note 169, at 203-204.

²⁴⁵ See *id.* at 186.

form of submitting data will be standardized, not the data required.²⁴⁶ Therefore, producers still need to comply with various approval application procedures in each market they wish to enter.²⁴⁷ There is the danger that the ICH will become another layer of regulation to pass, another level of red tape to break through, increasing the time from development to marketing.²⁴⁸

Echoing concerns about harmonization as a goal, consumer watch groups decry the lack of input from interested individuals and affected communities, which they claim results from industry-dominated working groups that meet behind closed doors.²⁴⁹ Even though standardization can be beneficial to both consumers and producers, consumers and producers are not necessarily benefited by the same types of standardization. For example, while elimination of duplicative regulatory requirements reduces costs to producers, producers may not pass these cost savings on to their consumers, and the elimination of some types of testing may result in less safe drugs reaching consumers.

Although anyone willing and able to pay the registration fee can attend ICH conferences,²⁵⁰ no formal mechanism exists to incorporate comments from the floor into the formal proceedings or to respond to such comments.²⁵¹ Beyond comments from the floor, there are no other means by which an individual not involved in the ICH Steering Committee or EWGs can present his opinion.²⁵² Further, although individual countries publish draft ICH guidelines and final ICH guidelines for comment pursuant to their internal regulatory

²⁴⁶See CDER, CBER, *Guidance for Industry: Submitting Marketing Applications According to the ICH-CTD Format—General Considerations* (2001), at <http://www.fda.gov/cber/ctd/ctdguid.htm>, visited March 11, 2002.

²⁴⁷See Moore and Cullen, *supra* note 5, at 102-107.

²⁴⁸See Kidd, *supra* note 169, at 186.

²⁴⁹See *Harmonization*, at <http://www.harmonizationalert.org/HarmBackgroundunder.htm>, visited January 21, 2002. See also, Miller, *supra* note 11, at 232.

²⁵⁰See Booth, *supra* note 8, at 212. Registration fees for the third conference in 1995 were approximately \$1330. See *id.* at 212 n.68.

²⁵¹See *id.* at 212. Registration materials for the third ICH conference specifically recognized “the importance of ensuring that the process of harmonisation is carried out in an open and transparent manner and that **ICH** discussions are presented in an open forum. Third **ICH**, Preliminary Program and Registration Forms (1995), *cited in* Booth, *supra* note 8, at 212.

²⁵²See *id.* at 213.

procedures, such feedback opportunity is not mandated by the ICH; draft guidelines only need be submitted for consultation to the regulatory body of each participating country.²⁵³ If a given country's procedure does not require notice and comment, no public opinion is solicited.

With regard to the scope of the ICH, critics claim that there are a whole host of issues to be resolved in the quest for international standardization that are not addressed by the ICH. The ICH deals mainly with scientific aspects of pharmaceutical regulation.²⁵⁴ However, as mentioned in discussing problems with standardization as an end goal, differences in cultural views of drugs must be confronted before a truly global market is achievable. For example, Asian views toward medicine and health lead to unwillingness to adhere to strict clinical testing protocols, leading Western nations to look upon the resultant data with skepticism. As another example, Americans are unwilling to accept any risk in pharmaceutical products. The ICH also fails to deal with the political and economic forces that influence the regulatory bodies in various countries.²⁵⁵ These issues have been impediments to harmonization of drug regulations across the EU, a less heterogeneous cultural and political area than the three ICH regions.²⁵⁶

The pace of implementation is another concern. Since the guidelines produced by ICH do not have the binding force of treaties, there is no mechanism for implementation other than each country pursuing its usual procedures for adopting regulations. As such, there is fear that implementation will be extremely slow.²⁵⁷ Also, the lack of enforcement power in the central ICH institutions create a vacuum which may be

²⁵³The FDA regulations do require publication of notice in the Federal Register and invites comments prior adoption of ICH guidelines. *See id.*

²⁵⁴*See* Kidd, *supra* note 169, at 202.

²⁵⁵*See id.* at 203.

²⁵⁶*See* Kidd, *supra* note 169, at 195.

²⁵⁷*See* Kanusky, *supra* note 19, at 695.

too tempting for member states to try and fill. Political wrangling and regional distrust would subvert the drive towards a faster drug approval process that optimally protects consumers.²⁵⁸

Specifically, some fear that the ICH will be plagued with the same problems that faced the EU's attempt to centralize and standardize its drug regulations. The EMEA, the EU's regulatory body for pharmaceuticals, is tasked with facilitating harmonization, not imposing it. Likewise, the ICH is envisioned as a provider of the infrastructure for cooperation. The fear is that the ICH will have just as much difficulty as the EU in getting countries to implement common procedures absent binding authority. While the EU might be forced to grant decision-making power to the EMEA, it is highly improbable that that would be an option for the ICH.²⁵⁹

IV. THE FDA AND STANDARDIZATION

A.

FDA's Attempts to Facilitate International Standardization

Within the United States, Congress has recognized that the imperative nature of increased efficiency in the drug approval process is as important as maintaining proper safety precautions.²⁶⁰ In the "findings" section of the Food and Drug Administration Modernization Act of 1997 (FDAMA), legislation intended to speed up the drug approval process, Congress acknowledged that prompt approval of safe and effective new drugs

²⁵⁸ See Eakin, *supra* note 58, at 222.

²⁵⁹ See Kidd, *supra* note 169, at 194-195.

²⁶⁰ See Littlefield and Hadas, *supra* note 113, at 35.

and other therapies is critical to the improvement of public health, so that patients may enjoy the benefits provided by these therapies to treat and prevent illness and disease.²⁶¹

The FDA has been tasked by Congress with facilitating international standardization of pharmaceutical regulations. In section 410 of the FDAMA, Congress mandated that the FDA pursue standardization.²⁶² In this legislation, the FDA is called on to support the Office of the United States Trade Representative... in meetings with representatives of other countries to discuss methods and approaches to reduce the burden of regulation and harmonize regulatory requirements if... such harmonization continues consumer protections consistent with the purposes of this Act.”²⁶³ The FDAMA added two objectives to the FDA’s mission: to participate... with representatives in other countries to reduce the burden of regulation, harmonize regulatory requirements, and achieve appropriate reciprocal arrangements; 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. ²⁶⁴

The FDA itself has manifested its commitment to international standardization through increased cooperation with the standardization process.²⁶⁵ The FDA leadership council recently added international consul-

²⁶¹FDAMA, §101 (1), *cited in* Littlefield and Hadas, *supra* note 113, at 35.

²⁶²*See* Pub. L. No. 105-115, 111 Stat. 2296 (1997), amending 21 U.S.C. §§ 301 et seq. (1994), *cited in* Shane M. Ward, *Global Harmonization of Regulatory Requirements for Premarket Approval of Autologous Cell Therapies*, 55 **Food & Drug L.J.** 225, 239-240 (2000).

²⁶³21 USCA § 383, *cited in* Ward, *supra* note 262, at 240.

²⁶⁴21 U.S.C. § 393 (FDAMA § 406 (amending FDCA § 903)), *cited in* Linda A. Suydam and Milan J. Kubic, *FDA’s Implementation of FDAMA: An Interim Balance Sheet*, 56 **Food & Drug L.J.** 131, 131 (2001). Similarly, in a recent CDER Mission Statement the FDA is urged to [p]articipate through appropriate processes with representatives of other countries to reduce the burden of regulation, harmonize regulatory requirements, and achieve appropriate reciprocal arrangements. FDA, *CDER 1998 Report to the Nation*, inside cover (1998), *cited in* Ward, *supra* note 262, at 240.

²⁶⁵*See* Eakin, *supra* note 58, at 222. Various motives have been posited for the increasing cooperation by the FDA in international standardization. Factors such as agency resource constraints, increased international trade of drug products, and political pressure exerted through mandatory trade agreements have been cited as driving FDA action. *See id.* Additionally, FDA actions have been attributed to FDA’s fear of losing its dominant position internationally in pharmaceutical regulation. Given its position as the regulator of the largest homogeneously regulated pharmaceutical industry and market, the FDA’s regulations have served as the basis for development and testing plans by producers. However, with the emergence of the even larger EU market regulated by the EMEA, there is the danger of EMEA regulations becoming the standard on which testing programs are based. If this were to occur, the pace of approval of drugs for the U.S. market would be further slowed in

tation and cooperation to the five fundamental principles of FDA's public health mission.²⁶⁶ The FDA also published a Policy on Standards regarding the agency's standardization efforts,²⁶⁷ in which it acknowledged that it must adhere to international standards in its domestic regulations, unless those standards are ineffective or inappropriate.²⁶⁸ The Policy emphasizes the importance of openness, transparency, and public involvement procedures for standard-setting in which the FDA is to participate.²⁶⁹ Furthermore, as of 1997, the FDA had published over fifty notices regarding draft ICH guidelines and other harmonization-related issues.²⁷⁰

To further the imperative of international standardization, the FDA has followed the suggestion of the President's Council on Competitiveness that the FDA increasingly rely on foreign data, and loosened its approval requirements to allow approval after the completion of one domestic clinical trial by an investigator trusted by the FDA.²⁷¹ The FDA thus acceded somewhat to the drive for acceptance of the products of foreign regulatory systems while still ensuring the safety and efficacy of proposed drugs.²⁷²

The FDA has also testified before Congress in support of standardization efforts.²⁷³ For example, to alleviate

the absence of standardization, as drugs developed to accord with EMEA guidelines would be subjected to additional testing before entering the U.S. market. The FDA might be engaging in standardization as a means to head off this increase in an already-criticized lengthy time to market. *See* Booth, *supra* note 8, at 207.

²⁶⁶*See* Suydam and Kubic, *supra* note 264, at 131. The other objectives of the FDA are: 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. *See id.*

²⁶⁷*See* Department of Health and Human Services, *Food and Drug Administration International Harmonization; Policy on Standards*, 60 **FR** 53078-01 (1995). This document covers all standardization efforts, including those for food, the Codex Alimentarius Commission and the Food Chemicals Codex, and the ICH. *See also* Booth, *supra* note 8, at 208-209. The Policy states that the FDA's participation in the ICH is covered by Title 21 of the Code of Federal Regulations, section 10.95, which provides mandatory standards for FDA participation in outside standards-setting activities. *See id.* at 211.

²⁶⁸Booth, *supra* note 8, at 209. However, the Draft Statement does not define criteria for deciding when standards are ineffective or inappropriate. *See id.*

²⁶⁹*See id.* at 210.

²⁷⁰*See* Booth, *supra* note 8, at 205-206.

²⁷¹*See* Miller, *supra* note 11.

²⁷²*See id.*

²⁷³That such testimony should be necessary is surprising given Congress' commitment to standardization as manifested in acts such as FDAMA. *See* text accompanying notes 260-264 for further examples of Congress' professed commitment to standardization. However, the House Commerce Committee, which oversees the FDA, has questioned the advisability of MRAs due to worries that MRAs will allow into the U.S. drugs approved under less exacting regulations than those imposed by the FDA. The Committee's concerns are at least in part a reflection of their constituents' zero tolerance for risk. Congress also does not want to be perceived as putting trade revenues above public health. *See also* Eakin, *supra* note 58, at 229.

fears about the advisability of U.S. commitment to MRAs, the FDA stressed in testimony before the House that the FDA initiated the drive toward shared inspections with the Europeans and that the FDA is not compromising its standards.²⁷⁴

B. Critique of FDA Participation in International Standardization

Despite the abovementioned actions on behalf of the FDA, some people still feel that the FDA is not taking appropriate action to facilitate standardization. The FDA has been criticized for its failure to wholeheartedly pursue international standardization. The FDA justified its reluctance to accept completely the results of foreign trials by citing the less detailed judgment and measurement of efficacy in foreign research protocols, the lack of familiarity of foreign researchers with close monitoring through recorded data, the reluctance of esteemed foreign researchers to follow guidance from sponsors, the cross-cultural differences in human interpretation of statistical norms and computer programs, the inclusion of less data in trial reports in other countries, and the lack of conviction of foreign companies in FDA standards.²⁷⁵

In all manifestations of its pursuit of standardization, including conclusion of MRAs; signing of MOUs; and participation in the ICH, the United States and the FDA have been criticized by adherents of standardization. Generally, U.S. and FDA participation is denigrated as superficial attempts to maintain power over international standard-setting regarding pharmaceuticals. For example, one commentator observed that it appeared to the EU at times that what 'MRA' meant to the U.S. was 'my regulations apply.'²⁷⁶ Similarly, critics decry the MOUs the FDA has entered into as just another means for the FDA to exert control over other markets, exporting its own standards rather than working towards standardization.²⁷⁷ FDA's pursuit

²⁷⁴ See Eakin, *supra* note 58, at 229.

²⁷⁵ See Miller, *supra* note 11, at 235.

²⁷⁶ See Eakin, *supra* note 58, at 229.

²⁷⁷ See *id.* at 228.

of MOUs with individual countries has been criticized as a means by which the FDA can say it is pursuing standardization, while still dictating the terms of inspection and safety levels.²⁷⁸ These claims are buttressed by the reality that under MOUs, the FDA's involvement in foreign regulations increases, as often foreign inspectors need training to be able to implement FDA standards abroad.²⁷⁹

Furthermore, critics claim that the FDA would prefer that it be in charge of standardization in place of the ICH or other international bodies.²⁸⁰ In line with that allegation, the FDA has been charged with not allocating sufficient resources to participation in the ICH, instead having employees work on ICH issues in addition to their other responsibilities.²⁸¹ Such staffing is said to be in line with the feeling of some people within the FDA that standardization takes away from the primary goal of the FDA of drug review.²⁸²

The actual process that the FDA uses to implement ICH guidelines has also been attacked. Criticism that the ICH process does not allow for enough input by affected parties other than government and industry groups has also been levied against the FDA in its procedure for adopting ICH guidelines. Although the FDA publishes draft guidelines for notice and comment before adopting the guidelines and then publishes the final guidelines for comment, this procedure has been decried as inadequate to allow for consumer input in the situation. The four to twelve weeks allowed for comments on the draft guidelines has been deemed inadequate for anyone not intimately involved in the development of such complex guidelines to master them to the degree necessary to comment intelligently on them. Such a process therefore only gives the illusion of soliciting input by affected parties not involved in the ICH conferences, while in reality such input is denied. This lack of actual input is exacerbated by the ICH protocol in which all substantive work on the guidelines are completed before the draft is published by the FDA. So even if comments were to be received by the

²⁷⁸ See *id.*

²⁷⁹ See Kidd, *supra* note 169, at 200.

²⁸⁰ See *id.*

²⁸¹ See *id.*

²⁸² See *id.* at 202.

FDA, the mechanism by which they might be incorporated into the ICH guidelines remains unclear.²⁸³ Thus, consumer groups, and to a more limited extent the OTC industry, are effectively bound by regulations in which they have no say.²⁸⁴

V. RECOMMENDATIONS

The international standardization of pharmaceutical regulations has the potential to benefit consumers and producers worldwide. However, unless certain impediments, detailed above, are overcome, the benefits of standardization may never be fully realized. Specifically, the various tools of standardization must be integrated into a cohesive system, input must be solicited from a broader spectrum of interested parties, and mechanisms for enforceability must be established.

Although mutual recognition and harmonization can be seen as complements, rather than as mutually exclusive, countries must be careful that these instruments do not work at cross purposes. Mutual recognition allows approval for sale of a product made to a harmonized set of specifications solely upon certification in the exporting country. Mutual recognition alone though, fails to provide one-step approval for multiple markets without harmonization or equivalence determinations.²⁸⁵ Due to this complementarity, even members of the ICH have continued to pursue MRAs. For example, Japan and the EU concluded an MRA effective

²⁸³ See Booth, *supra* note 8, at 216.

²⁸⁴ See *id.* at 217.

²⁸⁵ See *Community External Trade Policy in the Field of Standards and Conformity Assessment*, 10-11, available at <http://europa.eu.int/comm/trade/pdf/mra1.pdf>, visited on April 3, 2002.

January 1, 2002, which requires them to recognize mutual safety and reliability certifications of manufactured goods in the pharmaceutical, telecommunications, chemicals, and household electrical appliance industries. Negotiations over this MRA were ongoing since the mid-1990s, the same period in which the ICH was being implemented.²⁸⁶

Despite their complementarity, MRAs can undermine harmonization. For example, critics of the FDA have accused it of using MRAs to extend its regulatory hegemony over the markets of other countries. If this is indeed the case, and the FDA is using MRAs in part to increase its worldwide power, such behavior will serve to undermine the efforts of the ICH, which are predicated on a group of equals working together. To avoid such a situation, it is important to ensure that MRAs, MOUs, and the ICH be coordinated in a cohesive system, perhaps under the larger rubric of the ICH structure.

Another way in which international standardization can be facilitated is through the broader solicitation of input on both the domestic and international level. As detailed above, complaints about the lack of opportunity to impact the standardization effort have been levied against domestic participation in standardization as well as against the international procedures.²⁸⁷ Consumers and countries outside the ICH system feel that decisions are being made that affect them without consideration of their input on the issues.

Lack of input by affected groups will hamper the public acceptance necessary for the international standardization process to forge ahead. Domestically, although the FDA can force regulations on the public to some extent, opponents are not without weapons. Legal challenges and the manipulation of public opinion can be affective tools of slowing down implementation of the fruits of the ICH. By allowing more input of affected groups into the process, the FDA would build public confidence that safety standards were being maintained and would serve to deter legal challenges to the U.S. adoption of ICH guidelines.²⁸⁸ On an international

²⁸⁶See *Japan, EU exchange notes on product certification*, **Japan Wkly. Monitor** (Pg. Unavail. Online) 2001 WL 29458616 (2001).

²⁸⁷See text on pp. 49-50 and 56.

²⁸⁸See Booth, *supra* note 8, at 223.

level, cultural differences that would hamper the applicability and acceptance of international standards could be dealt with by soliciting opinions of diverse countries in the process of creating the standards.

The creation of enforcement mechanisms is a third major way by which international standardization can be facilitated. Development and implementation of MOUs, MRAs, and ICH guidances are slow. Currently, all standardization activity is on a voluntary basis, and the resulting agreements are non-binding. Going forward, it will be important for standardization activities to be encapsulated in a multilateral treaty with binding force. There should be a dispute resolution mechanism too, to address issues that arise. The “political commitments” currently in place need to be given the force of law. A possible model for an enforcement system would be that of Codex, which coopts the WTO dispute settlement process.

VI. CONCLUSION

As detailed above, efforts at standardization are intended to benefit consumers and pharmaceutical producers. Elimination of duplicative requirements is intended to allow consumers faster access to new treatments at lower cost while still ensuring product safety. Producers will be able to cut costs by reductions in the costs of compliance with multiple regulatory structures and increase profits by reducing time to market. These effects are mutually enforcing in many ways; if the cost of producing drugs is decreased with the reduction of regulatory requirements, producers can charge less for medicines or allocate some of the money saved to research and development.

Globalization is happening. Standardization of pharmaceutical regulations is progressing under the status quo of MRAs, MOUs, and the ICH. However, the pace of standardization is relatively slow. MRAs and

MOUs are piecemeal tools that bring about incremental change. While the ICH is more programmatic and encompasses the three major pharmaceutical producing countries, it provides a cumbersome, slow-paced process, that produces standards that are ultimately unenforceable.

To increase the pace of standardization, the MRA and MOU models need to be incorporated into the ICH and the ICH needs to be made binding on the parties. Furthermore, increased participation by non-member nations and consumer groups will facilitate acceptance of the results of the standardization process. The way in which Codex standards are given teeth through the WTO is a possible example of a way to make ICH guidelines binding on member states. Adopting these recommendations will allow the international community to reap more rapidly the full benefits of international standardization of pharmaceutical regulations.

THE NEED FOR COMPREHENSIVENESS AND INCREASED ENFORCEABILITY IN THE
STANDARDIZATION OF INTERNATIONAL PHARMACEUTICAL REGULATIONS

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