

COMMENT

WHAT IS PAST IS PROLOGUE: THE INTERNATIONAL CONFERENCE ON HARMONIZATION AND LESSONS LEARNED FROM EUROPEAN DRUG REGULATIONS HARMONIZATION

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1. INTRODUCTION

The pharmaceutical industry has experienced unprecedented changes over the past few decades. The advent of advanced biotechnology has made possible unparalleled progress in the development of new drugs and other medical treatments and technologies. Given this rapid rate of technological advance, regulatory agencies throughout the world have struggled to keep pace and maintain their vigilant protection of public health and safety. In recent years, many commentators, particularly those with industry ties, have criticized regulators for overburdening the pharmaceutical industry and hindering its ability to develop and market new drugs. This pressure to reform has resulted in a number of initiatives attempting to address these concerns without crippling the ability of regulatory agencies to protect public safety.

One such initiative is the movement to harmonize pharmaceutical regulations¹ across international jurisdictions. A

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¹ The term *pharmaceutical regulations* as used here refers to administrative regulations promulgated by governmental bodies that govern the research and

particularly promising exemplar of this movement has been the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use ("ICH"), an attempt to improve harmonization between the three dominant zones of new drug development: the United States, Europe, and Japan. On November 15, 2003, representatives from the pharmaceutical industries and regulatory agencies of these three nations, as well as other interested parties, concluded a meeting in Osaka, Japan, the sixth meeting of the ICH. One of the major topics of discussion at this meeting was the status and future of efforts to implement concrete ICH proposals for harmonization. Of particular note is the effort to instate a standard form in all three zones for the application for new drug marketing authorization, the Common Technical Document ("CTD").²

The ICH has been heralded as an exciting step in addressing the challenges to the global pharmaceutical industry. It enjoys considerable support from the industry as it can potentially reduce the cost of obtaining new drug marketing authorizations in the three most lucrative markets. However, as this Comment will show, significant obstacles await the ICH and the harmonization movement.

A useful comparison may be drawn to the experience of the European Union³ ("EU") in their own efforts to harmonize new drug development regulations within the European zone. The

development ("R&D"), sale, manufacturing, and use of pharmaceutical products. Other equivalent terms used throughout this Comment include *medicines regulations*, *drug development regulations*, and *drug regulations*. The scope of this Comment does not include the differences between regulations governing new drugs, new formulations or uses of previously approved drugs, generic versions of previously approved drugs, or other classes of products produced by pharmaceutical companies—including biologics, vaccines, blood products, etc.—which are generally regulated by the same agencies, or in a similar manner, as pharmaceutical drugs. Likewise, any use of the terms *regulations* or *regulatory agencies* only refers to those relevant to the pharmaceutical industry, such as the U.S. Food and Drug Administration ("FDA").

² See discussion *infra* Section 4.2.

³ The European Union ("EU") was only formally established with the Treaty of Maastricht in 1992, replacing the European Communities. See generally TREATY ON EUROPEAN UNION, 1992, O.J. (C 191) 1 (1992) [hereinafter TREATY OF MAASTRICHT] (establishing the European Union). Although the creation of the EU certainly had momentous legal implications beyond those of the Communities, the differences between the two bodies are not relevant to this Comment except as discussed in Section 3. Thus this Comment refers to the acts and laws of the EU as inclusive of those of the Communities.

result of these efforts has been a strongly centralized process for garnering marketing authorizations for new drugs with a great deal of authority resting in a supranational body, the Committee on Proprietary Medicinal Products ("CPMP"). Given a number of factors, most notably political and economic concerns, this level of centralization is perhaps unlikely to be the end result of the ICH. However, the European experience indicates that less robust regimes may ultimately prove unsuccessful.

At the core of any analysis of the ICH, or international harmonization as a whole, must be the recognition that pharmaceutical industry concerns are the predominant driving force behind developments in this area. This is apparent from the European experience as well as in the rationales typically given in support of the ICH and international harmonization. A key conclusion that must be drawn then is that mutual recognition,⁴ an industry priority, is of vital importance to the harmonization effort. With these facts in mind, the steps necessary for the success of the ICH become clearer, and its future prospects are more easily analyzed.

This Comment examines the future prospects of the ICH by analyzing the harmonization process in Europe. Section 2 will discuss the rationales behind the harmonization movement and the important economic concerns underlying them. Section 3 then scrutinizes the EU's experience with harmonization, which culminated in the so-called decentralized and centralized procedures instated in 1995. Section 4 then turns to the ICH, analyzing the similarities and differences between the ICH and the European experience, particularly the disparate national interests of the three parties arising from political and economic concerns. Section 5 discusses the conclusions that can be drawn from the comparison of the ICH with the EU experience and the key considerations in the future success of the ICH initiative. Lastly, Section 6 offers a final summary perspective.

2. RATIONALES FOR INTERNATIONAL HARMONIZATION

The call for the international harmonization of pharmaceutical regulations is a relatively recent phenomenon. As recently as 1985,

⁴ The terms *mutual recognition* and *reciprocal approval* are used more or less interchangeably and refer to the granting of marketing authorization for a drug based primarily on the positive assessment and marketing approval of the drug by another nation (i.e. without a full-scale independent assessment of the drug).

for example, the U.S. Food and Drug Administration ("FDA") did not approve applications for marketing authorizations based solely on research data gathered in clinical trials performed outside the United States.⁵ The EU's groundbreaking efforts to harmonize regulations within Europe really only began in the mid-1970s with the introduction of the now-defunct CPMP procedure.⁶ The ICH itself was only first convened in 1990.⁷ Considering that modern pharmaceutical regulation began as early as the 1930s, and more primitive regulation earlier still, harmonization is a relative latecomer.

The clamor for harmonization of regulations across national boundaries has become substantial with the increased globalization of the industry, a trend that has gained momentum in recent years.⁸ Mounting pressure for harmonization has also coincided with rising costs for pharmaceutical research and development ("R&D"), a situation many blame, at least partly, on overregulation by national regulatory agencies such as the FDA.⁹

⁵ See *New Drug and Antibiotic Regulations*, 50 Fed. Reg. 7452, 7453 (Feb. 22, 1985) (to be codified at 21 C.F.R. § 314.106) (explaining the basis for new FDA regulations which, for the first time, permitted marketing authorizations based solely on foreign clinical data).

⁶ See *infra* Section 3.2.

⁷ See *infra* Section 4.1.

⁸ The last decade has been witness to considerable consolidation in the pharmaceutical industry, resulting in domination by large multinational corporations that span continents. For example, Swedish giant Pharmacia A.B. and the Upjohn Company in the United States announced a merger in 1995 that formed what was then the ninth largest drugmaker in the world. Louis Uchitelle, *Aiming at H.M.O.'s, Upjohn Agrees to \$13 Billion Merger*, N.Y. TIMES, Aug. 21, 1995, at A1. U.K. goliaths Glaxo Wellcome and SmithKline Beecham followed suit, announcing in 2000 their intention to merge and become the world's largest drug company, GlaxoSmithKline ("GSK"), run from a new operational base in the United States. David Pilling, *Glaxo, SB to Announce Deal Today*, FIN. TIMES, Jan. 17, 2000, § 1, at 1. GSK now has manufacturing centers in thirty-seven countries and conducts R&D in seven different countries. GlaxoSmithKline, *About GlaxoSmithKline*, at <http://www.gsk.com/about/about.htm> (last visited Feb. 21, 2005). Other global mergers and acquisitions include: Astra (Swed.) merging with Zeneca (U.K.) to form AstraZeneca (U.K.); Roche (Switz.) acquiring Syntex (U.S.), then Boehringer Mannheim (F.R.G.), then partnering with Chugai (Japan); and Hoechst (Ger.) with Marion Merrell Dow (U.S.), then Rhone-Poulenc Rorer (Fr.), to form Aventis (Fr.). IMS Health, *M&A Drives Decade of Change*, Apr. 25, 2001, at http://www.ims-global.com/insight/news_story/0104/news_story_010425.htm.

⁹ See, e.g., MEIR STATMAN, *COMPETITION IN THE PHARMACEUTICAL INDUSTRY: THE DECLINING PROFITABILITY OF DRUG INNOVATION* 61-62 (1983) (contending that the high costs of complying with FDA requirements prevents drug companies from effectively conducting R&D).

A variety of reasons have been offered by commentators to promote the cause of harmonization. Among the most compelling are: (1) lowering new drug development costs for pharmaceutical companies; (2) reducing the time necessary to bring new drugs to market—the so-called drug lag phenomenon—thereby providing new treatments to the public faster; (3) increasing international cooperation in pharmaceutical industry regulation, thus improving regulatory efficiency and expertise; and (4) eliminating unnecessary duplication of clinical trials on human populations, thus minimizing risks to research subjects and assuaging ethical concerns. As these rationales are examined in turn, the strong influence of industry concerns will become apparent in each.

2.1. Lowering Drug Development Costs

Research and development in the pharmaceutical industry is among the most costly of any industry, both in terms of gross expenditures and percentage of operating budgets. The situation in the United States is representative; in 2000, the pharmaceutical industry was one of only five individual manufacturing industries in the United States that spent \$10 billion or more on R&D, a distinction it shared with only two others in 1999.¹⁰ For the period between 1997 and 2000, the pharmaceutical industry was the only individual American manufacturing industry with average R&D spending in double digits as a percentage of net sales, which was also over three times the average for all U.S. manufacturers.¹¹

Attempts to quantify the average cost of bringing a new drug to market have been somewhat controversial. Recent estimates for the United States have suggested figures exceeding \$800 million per new drug.¹² Although criticized, the Pharmaceutical Research

¹⁰ NAT'L SCI. FOUND., RESEARCH AND DEVELOPMENT IN INDUSTRY: 2000, at 34 tbl. A-7 (2003), available at <http://www.nsf.gov/sbe/srs/nsf03318/pdf/nsf03318.pdf>.

¹¹ *Id.* at 74 tbl. A-20.

¹² See, e.g., Joseph A. DiMasi et al., *The Price of Innovation: New Estimates of Drug Development Costs*, 22 J. HEALTH ECON. 151, 166 (2003) (estimating the costs at \$802 million). But see PUBLIC CITIZEN, RX R&D MYTHS: THE CASE AGAINST THE DRUG INDUSTRY'S R&D "SCARE CARD" 3-4 (2001) (arguing that actual costs are approximately \$110 million), available at <http://www.citizen.org/documents/ACFDC.PDF>. The debate over how the cost of new drug R&D should be calculated is an enormous topic unto itself. Groups like Public Citizen have sharply criticized the DiMasi study, which has become a favorite of the pharmaceutical industry. *Id.* Indeed, some of their criticisms may be valid, such as the fact that the DiMasi estimate does not discount for taxes. On the other hand, the Public Citizen calculation may be overly simplistic and not reflective of

and Manufacturers of America ("PhRMA") published an estimate in 2001 of \$500 million per new drug, which seems to be something of a median figure.¹³ Regardless of which figure is used, it is clear that the costs are considerable. Furthermore, most estimates indicate that these costs are only climbing.¹⁴

An important component of these costs is the high risk of new drug development, which endangers return on investment. Given that a pharmaceutical product typically cannot be sold without a marketing authorization issued by the national regulatory authority of the jurisdiction, failure to win approval essentially scraps all of the company's investment in the development of that product. Of every 5,000 medicines tested for potential sale in the United States, for example, only five reach clinical trials and only one receives marketing authorization.¹⁵ To compound these risks, only three in every ten drugs receiving marketing authorization result in sufficient revenue to recoup the average cost of R&D.¹⁶

true cost over time since, for example, it baldly refuses to factor in opportunity cost of capital. *Id.* at 28.

¹³ PHARM. RESEARCH AND MFRS. OF AMERICA, PHARMACEUTICAL INDUSTRY PROFILE 2000, at 2 (2001).

¹⁴ See Henry Grabowski, *Pharmaceuticals: Politics, Policy, and Availability: Patents and New Product Development in the Pharmaceutical and Biotechnology Industries*, 8 GEO. PUB. POL'Y REV. 7, 9-11 (2003) (calculating an annual increase in R&D costs of 7.4% over inflation). Compare OFFICE OF TECH. ASSESSMENT, PHARMACEUTICAL R&D: COSTS, RISKS, AND REWARDS 72 (1993) (estimating costs between \$140 million and \$194 million per drug for drugs that entered clinical trials from 1970 to 1982), available at <http://www.wws.princeton.edu/cgi-bin/byteserv.prl/~ota/disk1/1993/9336/9336.PDF>, and Joseph A. DiMasi et al., *Cost of Innovation in the Pharmaceutical Industry*, 10 J. HEALTH ECON. 107, 107-09 (1991) (estimating \$231 million per drug in the same period), with PHARM. RESEARCH AND MFRS. OF AMERICA, *supra* note 13 (estimating \$500 million in 2001), and DiMasi et al., *supra* note 12, at 166 (estimating \$802 million in 2000).

¹⁵ PHARM. RESEARCH AND MFRS. OF AMERICA, WHY DO PRESCRIPTION DRUGS COST SO MUCH 2-3 (2000), available at <http://www.phrma.org/publications/publications/brochure/questions/questions.pdf>; see also Ken Flieger, *Testing Drugs in People*, in AN FDA CONSUMER SPECIAL REPORT: FROM TEST TUBE TO PATIENT: NEW DRUG DEVELOPMENT IN THE UNITED STATES, Jan. 1995, at 8 (reporting that only twenty percent of drugs submitted to the FDA are eventually approved for marketing). Clearly, the more dramatic cutoff occurs before submission to the FDA with the Pharmaceutical Research and Manufacturers of America ("PhRMA") reporting that only 0.1% of new drug formulations are ever submitted to the agency. However, many of the decisions a company makes to *not* submit a new drug to the FDA for review are based on its belief that the risk of the drug not passing muster — due to extremely exacting regulatory standards — is too high to justify the high costs of the FDA approval process.

¹⁶ PHARM. RESEARCH AND MFRS. OF AMERICA, *supra* note 13, at 2-3. See Henry Grabowski et al., *Returns on Research and Development for 1990s New Drug*

Due to these costs, the industry expends enormous effort to pressure regulators and lawmakers for reform of regulations to mitigate costs.¹⁷ Harmonization promises a number of benefits for industry in this area, mostly by eliminating duplicative efforts to obtain marketing authorizations in multiple jurisdictions and streamlining the overall approval process. As the other rationales are examined, it will become clear that the industry's desire to reduce costs forms an economic basis for virtually all of them.

2.2. Reducing Drug Lag¹⁸

The time it takes for a new drug to go from inception to the consumer is protracted due to the regulatory goals of ensuring safety, quality, and efficacy. Reduction of drug review times has thus been a focus of the pharmaceutical regulatory community in recent years. In Europe, both national regulatory agencies and supranational bodies overseeing the EU's harmonized regulatory processes have labored to reduce drug review times.¹⁹ The United States has followed suit, making faster drug approvals a priority.²⁰ The need for such reform was clear. In the United States, for example, a new drug developed in the early 1990s would take the better part of a decade before reaching market and could take as long as twenty years.²¹

Introductions, 20 PHARMACOECONOMICS 11, 22-23 (3d Supp. 2002) (graphing distributions of returns compared with research and development costs).

¹⁷ A recent study found that the U.S. pharmaceutical and healthcare industries spent \$237 million on lobbying efforts in 2000 alone. Steven H. Landers & Ashwini R. Sehgal, *Health Care Lobbying in the United States*, 116 AM. J. MED. 474, 474-75 (2004). This constituted 15% of the total amount spent on federal lobbying in the United States, the largest amount of any industry. *Id.* Of this figure, the largest component was the expenditure of \$96 million by pharmaceutical and health product companies. *Id.* at 475.

¹⁸ The "drug lag" phenomenon has been the subject of a great deal of scholarship. Essentially, the term refers to the lag between development of a new drug and its delivery to market, namely the time required to obtain marketing approval from regulatory authorities. See, e.g., BARUCH A. BRODY, ETHICAL ISSUES IN DRUG TESTING, APPROVAL, AND PRICING: THE CLOT-DISSOLVING DRUGS 164-65 (1995); Sam Peltzman, *An Evaluation of Consumer Protection Legislation: The 1962 Drug Amendments*, 81 J. POL. ECON. 1049 (1973) (finding a net negative impact on consumers as a result of the 1962 drug amendments).

¹⁹ See discussion *infra* Section 3.

²⁰ See BILL CLINTON & AL GORE, REINVENTING REGULATION OF DRUGS AND MEDICAL DEVICES 2-5 (1995) (declaring that shortening review times for new drugs and medical devices, as well as eliminating "unnecessary regulation," would be priorities in reforming FDA regulations).

²¹ See Flieger, *supra* note 15, at 10 (breaking down the time required for each

Some benefits of a quick turnaround in approving drugs are obvious. First and foremost, reducing the delay permits the more rapid supply of new drugs to the patients who need them. This expedited turnaround would minimize pain and suffering and even save lives if the condition to be treated is terminal. Furthermore, earlier availability of drugs could potentially lower health care costs.²² These benefits are the ones most often cited by government officials and regulators in recent years to justify efforts to reduce domestic drug approval times.²³ Proponents of harmonization argue that better meshing regulatory systems across borders would hasten the availability of drugs internationally in much the same way. This is a logical proposition; harmonization would reduce drug approval time in the aggregate if marketing authorizations must be sought from multiple nations.

Other benefits to reducing drug lag are not quite as obvious but may in fact be more influential in the push for harmonization. An important example lies at the nexus between drug approval times and patent rights. Many drugs, particularly cutting-edge medicines, are granted patent protection even before entering the regulatory approval process.²⁴ Every day spent attempting to obtain marketing authorization for a drug is a day not spent

stage of drug development in the United States from inception through the FDA approval process); *see also* DiMasi et al., *supra* note 12, at 164-66 (estimating an average of 90.3 months from the start of clinical testing until marketing approval and 52.0 months for preclinical development, a total of 142.3 months or nearly twelve years).

²² U.S. healthcare costs in 2000 reached an estimated \$1.3 trillion, nearly 15% of GDP. *American Health Care Is the Best in the World—If You Can Get It*, *ECONOMIST*, Sept. 28, 2000. Of this amount, \$112 billion comes from prescription drug expenditures alone, a figure growing at 10% per annum. *Id.* Faster drug approvals could potentially lower these costs by lowering development costs for manufacturers and spurring competition.

²³ For example:

Millions of Americans are suffering from diseases that may be curable or at least manageable as a result of technologies in development now. From a public health standpoint, making it simpler and more straightforward to translate all these investments into valuable products can have a substantial positive impact on the health of the nation, and can improve access to needed care as well.

FOOD AND DRUG ADMINISTRATION, STRATEGIC ACTION PLAN: PROTECTING AND ADVANCING AMERICA'S HEALTH 11 (2003).

²⁴ Gerald J. Mossinghoff, *Overview of the Hatch-Waxman Act and Its Impact on the Drug Development Process*, 54 *FOOD & DRUG L.J.* 187, 192 (1999); Grabowski, *supra* note 14, at 11.

reaping commercial gain from its sale, effectively cutting the term of the patent.²⁵ Therefore, reduced drug lag can substantially increase the returns on investment for a pharmaceutical company, and harmonization multiplies this effect for any drug sold in multiple markets internationally. Clearly, this is another appealing consequence of reduced approval times for the industry.

2.3. Increasing Cooperation Among Regulatory Agencies

One tremendous advantage of increased cooperation and harmonization between regulatory agencies worldwide would clearly be heightened efficiency of the review process. In the case of the participating nations of the ICH, for example, a fully harmonized process would allow regulators in the United States, Europe, and Japan to work in concert to minimize needless duplication, more efficiently allocate resources, and streamline the review process. As compared to the current regime in which three separate agencies—and possibly more given the complex multinational system in place in Europe²⁶—evaluate each drug separately, the advantages in efficiency are obvious.

²⁵ Grabowski, *supra* note 14, at 11. Since patents grant a limited monopoly on the patented technologies, shorter effective patent life (“EPL”) cuts into the most lucrative portion of a drug’s commercial lifetime. The average EPL of pharmaceutical patents for drugs developed in the 1990s was roughly twelve years, significantly less than the original term of twenty years. *Id.* at 12. The losses incurred from failing to take advantage of a portion of the term of a pharmaceutical patent can be considerable. Based on data from the 1990s, one study reported mean worldwide sales rising rapidly from just under \$100 million per year at market introduction to a peak of over \$450 million per year before patent expiry—namely the introduction of competition—decreases sales as market share is lost and price competition has its effect. Grabowski et al., *supra* note 16, at 17, fig.3. For the most lucrative drugs, peak sales exceeded \$2.5 billion per year worldwide prior to patent expiry. *Id.* at 17-18, figs.2, 4.

In order to mitigate this patent limiting effect, all three participating zones of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (“ICH”) have passed various legislation to restore some patent protection by artificially extending patent life. *See, e.g.,* Drug Price Competition and Patent Restoration Act, 35 U.S.C. § 156 (2004) (permitting the extension of patents that have been effectively reduced by regulatory review periods, but by no more than five years and to a maximum of fourteen years after the date of approval). However, there have been allegations that the U.S. Patent and Trademark Office (“PTO”) has been far from liberal in granting such extensions. *See* Ronald L. Desrosiers, Note, *The Drug Patent Term: Longtime Battleground in the Control of Health Care Costs*, 24 NEW ENG. L. REV. 115, 141 (1989) (stating that as of 1988, the PTO had only granted the full extension allowed by law in two out of ninety cases).

²⁶ *See* discussion *infra* Section 3.2.

A more subtle but crucial aspect of increased cooperation is the advantage of pooling intellectual resources in a harmonized approach. One of the greatest challenges for any agency regulating a highly technical field is maintaining a high enough level of scientific expertise within the agency in order to properly evaluate state-of-the-art technology. This problem is an acute one for agencies regulating the pharmaceutical industry. Many have established special scientific advisory committees, such as the United Kingdom's Committee on Safety of Medicines ("CSM") or Sweden's Board of Drugs ("BOD"), whose expertise is consulted on applications for marketing approval, particularly those for new drugs.²⁷ The FDA established both the Center for Drug Evaluation and Research ("CDER") and the Center for Biologics Evaluation and Research ("CBER") to serve this function in the United States.²⁸ Japan's equivalent body is the National Institute of Health Sciences ("NIHS").²⁹

Successful harmonization as envisioned by the ICH could certainly assist the participating regulatory agencies by increasing communication and the sharing of knowledge between regulators as well as their scientific advisors. By pooling these intellectual resources, regulators could improve the speed and expertise with which they assess the merits of drug marketing applications. They would also be better equipped to offer guidance to companies at all stages of the process.

While obviously beneficial to regulators, these considerations present advantages to the industry as well. Inefficiency in agency

²⁷ See JOHN ABRAHAM & GRAHAM LEWIS, REGULATING MEDICINES IN EUROPE 60-71 (2000) (describing the role of scientific advisory bodies in the British and Swedish regulatory systems).

²⁸ See FOOD AND DRUG ADMINISTRATION, IMPROVING PUBLIC HEALTH: PROMOTING SAFE AND EFFECTIVE DRUG USE (2003) (describing the responsibilities of the Center for Drug Evaluation and Research ("CDER"), including expert scientific analysis of all new drugs), at <http://www.fda.gov/opacom/factsheets/justthefacts/3cdcr.pdf>; FOOD AND DRUG ADMINISTRATION, CBER—ABOUT US (2003) ("[R]eview of new biological products [by the Center for Biologics Evaluation and Research ("CBER")] . . . requires evaluating scientific and clinical data submitted by manufacturers to determine whether the product meets CBER's standards for approval."), available at <http://www.fda.gov/cber/about.htm>. Simply put, chemically synthesized pharmaceuticals fall under the purview of CDER while biologics, medicinal products derived from living sources, are governed by CBER.

²⁹ See NAT'L INST. OF HEALTH SCI., MISSION STATEMENT (describing the purpose of the NIHS, including "evaluating the quality, efficacy and safety of . . . food, drugs, and agricultural chemicals"), available at http://www.nihs.go.jp/aboutnihs/nihs_pamphlet/p1.html (last visited Feb. 21, 2005).

action has been a prime complaint of the industry for years. In addition, greater scientific expertise and guidance from regulatory agencies would certainly be welcomed by the pharmaceutical industry as it would introduce greater certainty in what is now a very risky enterprise.³⁰

2.4. Eliminating Unnecessarily Duplicative Clinical Trials

It is undisputed scientific fact that sound research into new medicines must include extensive clinical trials on human populations. In fact, such trials are required to some degree under virtually all modern regulatory schemes controlling drugs and medicinal products worldwide.³¹

However, it is clear that clinical trials pose risks for the research subjects involved,³² which is why they are heavily regulated.³³ Eliminating unnecessarily duplicative trials is thus an ethical imperative.³⁴ Recent ethical controversies arising from clinical

³⁰ See discussion *supra* Section 2.1 (noting the perils and costs of the FDA approval process).

³¹ See, e.g., Applications for FDA Approval to Market a New Drug, 21 C.F.R. § 314.50 (2003) (requiring results of clinical trials in applications for FDA approval); Food and Drug Regulations Under the Food and Drugs Act, ch. 870, C.R.C. § C.08.002(2)(g)-(h) (2004) (Can.) (requiring test results to prove safety and “clinical effectiveness” in new drug submissions); Medicines Regulations (1971) SI 973, sched. I, pt. I, ¶ 27 (Eng.) (requiring reports of all studies “relevant to the assessment of the safety, quality or efficacy of the medicinal product” in applications for a license).

³² The dangers faced by clinical trial participants have been the subject of intense scrutiny for much of the last century. The topic was thrust to the forefront following World War II, as evidence of unethical human experimentation performed by Nazi doctors on unwilling Jews was uncovered. BARUCH A. BRODY, *THE ETHICS OF BIOMEDICAL RESEARCH* 31-32 (1998). The exposure of the forty-year U.S. Public Health Service (“PHS”) study of the long-term effects of syphilis in poor African American men—the so-called Tuskegee syphilis study—caused a similar stir. See *id.* at 33 (discussing the ethics of the Tuskegee syphilis study). See generally JAMES H. JONES, *BAD BLOOD: THE TUSKEGEE SYPHILIS EXPERIMENT* (new and expanded ed. 1993) (recounting in detail the circumstances and impact of the Tuskegee syphilis study). Other such incidents included the Halushka case in Canada and the Auckland cervical cancer studies in New Zealand. See BRODY, *supra*, at 33 (discussing incidents of human experimentation gone awry outside the United States).

³³ See, e.g., Council Directive 2001/20/EC, 2001 O.J. (L 121) 34 (detailing requirements for EU clinical trials regulation), available at http://europa.eu.int/eur-lex/pri/en/oj/dat/2001/l_121/l_12120010501en00340044.pdf; The Medical Products Agency’s Provisions and Guidelines on Clinical Trials of Medicinal Products for Human Use, LVFS 2003:6 (Swed.) (implementing EU requirements in Sweden), available at http://www.mpa.se/eng/lvfse/LVFSe_2003-6.shtml.

³⁴ For a detailed discussion of the ethical considerations of human clinical

research on new medicines, particularly those conducted in developing nations,³⁵ have emphasized the importance of

trials, see BRODY, *supra* note 32, at 139-60 and J.K. MASON & R.A. MCCALL SMITH, *LAW AND MEDICAL ETHICS* 351-68 (4th ed. 1994).

One of the most contentious areas in the debate on international medical research ethics is that of informed consent. Although this issue is well documented in the domestic tort law field, the scientific profession continues to wrestle with it as research becomes increasingly complex and international in scope. Two aspects of the issue are of particular importance to the topic of international medicines regulation: (1) what constitutes *informed* consent when uneducated, unsophisticated people are the subjects of a clinical trial; and (2) whether research subjects are truly able to make a voluntary choice to participate when their socioeconomic condition prevents them from access to any alternative form of treatment. These concerns manifest themselves notably in the case of research done in developing nations. For an in-depth discussion of the issue of informed consent in an international context, see BRODY, *supra* note 32, at 43-48 and MASON & MCCALL SMITH, *supra*, at 359-62.

If international regulatory regimes are to move toward greater acceptance of foreign clinical data, the parameters of such acceptance must be adequately defined in order to prevent frustration of regulatory goals, namely the protection of research subjects. The limited nature of the harmonization espoused by the ICH—involvement of only developed nations—could allow for a partition along the lines of ICH membership, perhaps providing for heightened deference to clinical studies performed in ICH zones rather than in other locales. Although not examined in detail in this Comment, the ICH has already begun to address the issue of informed consent along with various other ethical issues. See EUROPEAN AGENCY FOR THE EVALUATION OF MEDICINAL PRODUCTS, NOTE FOR GUIDANCE ON GOOD CLINICAL PRACTICE, CPMP/ICH/135/95 at 1 (May 1, 1996) (“[The ICH Good Clinical Practice Guideline] is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects . . . a unified standard for [ICH participating nations] . . .”) [hereinafter GCP GUIDELINE], available at <http://www.emea.eu.int/pdfs/human/ich/01359sen.pdf>.

Another ethical issue of particular relevance to international medicines regulation is that of independent review of clinical trial protocols. In most developed nations, such as those participating in the ICH, clinical trials are required to undergo independent evaluation by institutional review boards (“IRBs”), who are responsible to the government to some extent. See, e.g., IND Content and Format, 21 C.F.R. § 312.23(a)(1)(iv) (2002) (requiring the approval and monitoring of an IRB for FDA approval of clinical trials); Institutional Review Boards, 21 C.F.R. §§ 56.101-.115 (2005) (outlining the form, function, and operations of IRBs). Obviously this type of review, as well as enforcement of the boards’ authority, is much more difficult when the trials are performed abroad. As with informed consent, the ICH has spoken on this issue. See GCP GUIDELINE, *supra*, Section 3 (setting the requirements for and functions of IRBs for ICH nations). However, in the future it could be feasible to take further steps, perhaps including direct cooperation between IRBs in ICH nations to expand the boundaries of their oversight.

³⁵ The most prominent recent controversy involved a series of clinical trials performed primarily in sub-Saharan Africa on the relative effectiveness of treatment regimens for Acquired Immune Deficiency Syndrome (“AIDS”)

adequately addressing clinical trials in any international regulatory regime.³⁶ Harmonization advocates argue that facilitation of

compared to an established regimen known as AIDS Clinical Trials Group Study 076 ("ACTG 076"). ACTG 076 was a treatment regimen using the drug zidovudine, better known as azidothymidine or AZT, to reduce the risk of perinatal transmission of AIDS. These studies, mostly funded by various national governments including the United States (through the National Institutes of Health ("NIH") or the Centers for Disease Control ("CDC")), raised a host of ethical issues regarding international clinical research, particularly if performed in developing nations. For an in-depth and highly publicized discussion of these issues, see Peter Lurie & Sidney M. Wolfe, *Unethical Trials of Interventions to Reduce Perinatal Transmission of the Human Immunodeficiency Virus in Developing Countries*, 337 NEW ENG. J. MED. 853 (1997), reprinted in AIDS: SOCIETY, ETHICS AND LAW 403 (Udo Schüklenk ed., 2001) [hereinafter Schüklenk, AIDS]; Harold Varmus & David Satcher, *Ethical Complexities of Conducting Research in Developing Countries*, 337 NEW ENG. J. MED. 1003 (1997), reprinted in Schüklenk, AIDS, *supra*, at 407; George J. Annas & Michael A. Grodin, *Human Rights and Maternal-Fetal HIV Transmission Prevention Trials in Africa*, 88 AM. J. PUB. HEALTH 560 (1998), reprinted in Schüklenk, AIDS, *supra*, at 411; Robert J. Levine, *The "Best Proven Therapeutic Method" Standard in Clinical Trials in Technologically Developing Countries*, 20 IRB: A REVIEW OF HUMAN SUBJECTS RESEARCH 5 (1998), reprinted in Schüklenk, AIDS, *supra*, at 415; and also see Peter Lurie et al., *Ethical, Behavioral, and Social Aspects of HIV Vaccine Trials in Developing Countries*, 271 JAMA 295 (1994), reprinted in Schüklenk, AIDS, *supra*, at 421.

³⁶ In response to the many ethical crises that have erupted—beginning with the conduct of Nazi researchers during World War II—numerous attempts have been made to codify an international standard for medical research ethics. The first was the Nuremberg Code, a set of ten ethical principles that were a part of the judgment of the tribunal against Nazi scientists in 1947. See GEORGE J. ANNAS & MICHAEL A. GRODIN, *THE NAZI DOCTORS AND THE NUREMBERG CODE: HUMAN RIGHTS IN HUMAN EXPERIMENTATION 2* (1992). The Nuremberg Code asserted as fundamental necessities in human research: (1) "voluntary [informed] consent," (2) minimization of risks for research subjects, and (3) that the societal benefits outweigh the risks. See *id.* at 2, paras. 1-2, 4-7. These tenets were embraced by the World Medical Association ("WMA") in the highly influential Declaration of Helsinki, which has been revised on several occasions, most recently in 2002. See *Declaration of Helsinki*, WMA Doc. 17.C (2004) (originally adopted in 1964 and amended in 1975, 1983, 1989, 1996, and 2000), available at <http://www.wma.net/e/policy/pdf/17c.pdf>. In addition, the Declaration of Helsinki espouses the use of IRBs, addresses the issue of incompetent subjects incapable of providing informed consent, and demands that the "best current" treatments be provided to all research subjects, including any receiving a placebo, at the conclusion of the study. *Id.* paras. 13, 24-26, 30. The 2002 revision sought to expound on the WMA's position on the use of placebo controls. See *id.* para. 29, n.1 (approving of the use of placebo controls but only with "extreme care"); cf. sources cited *supra* note 35 (discussing the ethical considerations of the use of placebo controls in ACTG 076 trials in Africa). Another notable attempt at an international research ethics code is that published by the Council for International Organizations of Medical Sciences ("CIOMS") in conjunction with the World Health Organization ("WHO"). See generally CIOMS/WHO, *INTERNATIONAL ETHICAL GUIDELINES FOR BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS* (2002) (providing extensive guidelines regarding clinical research practices based on the principles of the

mutual acceptance of clinical data would eliminate unnecessary clinical studies, thus reducing these ethical concerns. This has been a major focus of the ICH to date, moving toward a mutual acceptance system that minimizes the need for companies to repeat clinical trials in each jurisdiction in which they intend to market their products.³⁷

Unfortunately, scientific concerns do limit the extent to which such harmonization can occur. Given the different demographics of the United States, Europe, and Japan, the applicability of clinical data from one zone to predicting safety and/or efficacy in another may be suspect. Differing genetic or other biologically relevant characteristics of a population can have an impact on a drug's effect.³⁸ Thus, while eliminating duplicative clinical trials is a worthwhile goal for harmonization efforts as a rule, some region-specific clinical testing may remain necessary.

These scientific limitations aside, the advantages of a lesser need for repetitive clinical trials are clear for the industry. Clinical trials are now the most costly expenses of pharmaceutical R&D³⁹ precisely because of the exacting standards imposed on them by regulatory authorities.⁴⁰ Furthermore, given the inherent risks involved in clinical trials of new medicines, excessive clinical testing could merely increase the risk of tort liability for injuries

Declaration of Helsinki with notable attention to issues of research conducted in developing nations), available at http://www.cioms.ch/frame_guidelines_nov_2002.htm. The ICH GCP Guideline is the offspring of these various codes. For another discussion of these standards and their international legal implications, see David P. Fidler, "Geographical Morality" Revisited: *International Relations, International Law, and the Controversy over Placebo-Controlled HIV Clinical Trials in Developing Countries*, 42 HARV. INT'L L.J. 299 (2001).

³⁷ See GCP GUIDELINE, *supra* note 34, at 1 ("The objective of this ICH GCP Guideline is to . . . facilitate the *mutual acceptance* of clinical data by the regulatory authorities in [ICH nations].") (emphasis added).

However, pre-ICH regulations did provide some opportunities for this sort of harmonization. See, e.g., *New Drug and Antibiotic Regulations*, *supra* note 5 (regarding the enactment of U.S. regulations permitting marketing authorizations based solely on foreign clinical data).

³⁸ Cf. Lurie & Wolf, *supra* note 35, at 296 ("[T]he possible existence of genetic, environmental, or nutritional cofactors for [Human Immunodeficiency Virus ("HIV")] infection that may vary from country to country require that phase III [clinical] trials be conducted in industrialized and developing nations.").

³⁹ See DiMasi et al., *supra* note 12, at 166-68, fig.2 (calculating the average capitalized cost per new drug of the clinical trial period at \$467 million, or 58.2% of the total cost per drug).

⁴⁰ See *supra* note 33 and accompanying text.

caused to research subjects.⁴¹ Therefore, the interests of industry are sure to be served if the number of clinical trials required is decreased.

3. HISTORY OF EUROPEAN HARMONIZATION

The EU is a loose confederation of Member States, each maintaining their basic sovereignty while vesting central EU bodies with enumerated authority to make decisions binding on all Member States.⁴² This organizational structure has resulted in a dual level system of regulation in many areas, including medicines regulation. First, each Member State retains a national regulatory agency, whose approval is still technically necessary for access to that nation's markets.⁴³ Second, at the supranational level, the European Agency for the Evaluation of Medicinal Products ("EMA") and the CPMP have evolved from the harmonization movement to address transnational regulatory issues.⁴⁴ An understanding of both levels is necessary to comprehend the issues faced by the EU in its push toward harmonization.

3.1. National Regulation in Europe

While legislation in European nations governing the development and sale of pharmaceutical drugs existed before the twentieth century, modern regulation in the form of national regulatory agencies emerged just prior to World War II in Scandinavia. The most notable such agency was the Department of Drugs ("SLA") of the National Board of Health and Welfare ("NBHW") formed by Sweden in 1935.⁴⁵ Swedish drug laws, even as early as the 1930s, were ahead of their time as they required the industry to demonstrate safety and efficacy of new drugs prior to

⁴¹ See LeRoy Walters, *Ethical Issues in the Prevention and Treatment of HIV Infection and AIDS*, 239 SCI. 597, 602 (1988) ("[T]he risk of litigation for research-related injury might be reduced in a non-U.S. setting [such as Africa].").

⁴² EUROPEAN COMMISSION, HOW THE EUROPEAN UNION WORKS 3-4 (2003), available at http://europa.eu.int/comm/publications/booklets/eu_documentation/06/en.pdf.

⁴³ See *infra* Section 3.1 (examining national-level medicines regulation in European countries).

⁴⁴ See *infra* Section 3.2 (examining medicines regulation at the EU level).

⁴⁵ Sweden, the United Kingdom, and Germany have had what are among the most influential national regulatory agencies in Europe for much of the twentieth century. Thus the history of medicines regulation in these three nations is discussed here as representative of the rest of Europe.

marketing approval by the SLA.⁴⁶ The SLA remained the central regulatory authority in Sweden until 1990 with the formation of the Medical Products Agency ("MPA").⁴⁷ One of the major early accomplishments of the MPA in the early 1990s was the drastic reduction of review times, a response to pressure from industry.⁴⁸ The MPA is considered among the agencies most receptive to industry concerns in Europe.⁴⁹

⁴⁶ See M.N.G. DUKES, *THE EFFECTS OF DRUG REGULATION* 9 (1985) (noting that the inclusion of efficacy criteria in Norwegian and Swedish pharmaceutical regulations predated those of most nations by roughly thirty years). Most nations at this point were predominantly concerned with product quality, namely that a product was what the manufacturer said it was. Sweden and Norway were the first countries in Europe to require that a product *do* what the manufacturer claimed it did. *Id.*

⁴⁷ ABRAHAM & LEWIS, *supra* note 27, at 68.

From the 1960s until 1981, the final authority on marketing approval for new drugs resided with the Board of Drugs ("BOD") though the Department of Drugs ("SLA") remained the agency responsible for evaluating new drug applications. The SLA would provide its analysis of new drug applications along with a recommendation for approval (or rejection) to the BOD, which would render the final decision to the applicant. The SLA regained its full authority in 1981, and the BOD has since been relegated to the scientific advisory role. The Medical Products Agency ("MPA") is notably different than the SLA in that it is now largely independent from the parent Ministry of Health and Social Affairs, in day-to-day operations, in a manner similar to the relationship between the FDA and the U.S. Department of Health and Human Services ("HHS"). *Id.* at 55-56, 68.

The MPA, and the SLA before it, has historically enforced its authority more easily compared to other nations' agencies given that all sales of medicines in Sweden are done through the state pharmacy company, Apoteksbolaget, since 1961. *Id.* at 57.

⁴⁸ *Id.* at 68. See generally discussion *supra* Section 2.2 (discussing the issue of drug lag and review times).

⁴⁹ Among the reasons why the MPA is seen as so closely tied to industry is the agency's heavy dependence on fees, a condition prevalent in many of Europe's national regulatory agencies. See *infra* Section 3.3. The MPA charges companies fees for its services in reviewing applications for marketing approval, rendering administrative guidance, overseeing clinical trial protocols, etc., as well as annual fees after authorizations have been granted. Medical Products Agency's Provisions and Guidelines on the Payment of Application and Annual Fees for Medicinal Products, LVFS 1995:12 (Swed.). This pecuniary link between the MPA and the industry gives pharmaceutical companies a powerful influence due to the nature of the EU's current mutual recognition system of supranational medicines regulation. The MPA and other national agencies compete with each other to serve as the agency of first approval, namely the agency that conducts the primary review of a given new drug application. See *infra* Sections 3.2-3. Since primary review permits the charging of larger fees, inter-agency competition arguably results in companies having a good deal of leverage, particularly given the dominance of a handful of monolithic multinational corporations in the industry. The MPA could thus understandably be reluctant to unnecessarily delay an

In 1943, the Nazi government in Germany banned the sale of any drugs not explicitly approved for sale by the government.⁵⁰ Its successor, the government of the Federal Republic of Germany, upheld the ban until it was ruled unconstitutional by the German Constitutional Court in 1959.⁵¹ The original justification for the ban given by the Nazi government was to protect national security, while the post-war government claimed the maintenance of the ban was due to its goal of protecting the public from unnecessary or dangerous drugs.⁵² Shortly after the lifting of the ban, the German Parliament (Bundestag) passed the German Drug Law (Arzneimittelgesetz, "AMG") of 1961, which established the Federal Health Ministry (Bundesgesundheitsamt, "BGA") as the national regulatory authority over the pharmaceutical industry.⁵³ AMG 1976 expanded the reporting requirements of pharmaceutical companies, mandated extensive drug testing, and directed the BGA to evaluate drugs based on assessments of safety and

application submitted by a company like Pfizer, for example, since doing so could discourage the company from selecting the agency for its many future applications. (However, this is not to say that the MPA is not still dedicated to ensuring the public health and safety of the Swedish people.)

The inter-agency competition phenomenon in European drug regulation in some ways resembles interstate competition in attracting corporate charters in the United States. Some allege that Delaware's dependence on its domination of the corporate charter "market" has resulted in a pro-corporate regulatory scheme in the state, the "race to the bottom" theory. See, e.g., Guhan Subramanian, *The Influence of Antitakeover Statutes on Incorporation Choice: Evidence on the "Race" Debate and Antitakeover Overreaching*, 150 U. PA. L. REV. 1795 (2002) (describing how states' eagerness to attract more incorporations through enacting antitakeover statutes results in a "race to the bottom").

⁵⁰ Arthur A. Daemmrich, *Regulatory Laws and Political Culture in the U.S. and Germany*, in REGULATION OF THE PHARMACEUTICAL INDUSTRY 11, 17-18 (John Abraham & Helen Lawton Smith eds., 2003).

⁵¹ *Id.* at 19-20, 26.

⁵² *Id.* at 18-19.

⁵³ Gesetz über den Verkehr mit Arzneimitteln (Arzneimittelgesetz), v. 16.5.1961 (BGBl. I S.533) [hereinafter AMG 1961]; see also ABRAHAM & LEWIS, *supra* note 27, at 50 (outlining the major points of AMG 1961). AMG 1961 was strengthened in 1964 following the thalidomide scandal, a pivotal event in the development of modern drug regulation. See Daemmrich, *supra* note 50, at 28-29 (discussing the aftermath of AMG 1961). However, these amendments were deemed inadequate in the prevailing political climate of the time, and the BGA's close ties to the industry were lambasted as a more robust regulatory system was put into place. *Id.* Different politics govern the direction of medicines regulation today, but the importance of politics in the issues of this area of law is a key consideration when contemplating its future. See discussion *infra* Section 4.

efficacy.⁵⁴ The BGA was disbanded in 1994, and its regulatory duties over medicines were given to the new Federal Institute for Medicinal Products and Devices (Bundesinstitut für Arzneimittel und Medizinprodukte, "BfArM"),⁵⁵ a move welcomed by the industry. Among the reasons given for the BGA's dissolution was the high dissatisfaction with the agency's lengthy review times.⁵⁶ The BfArM has dramatically reduced review times and has been credited with repairing relations between the government and the industry.⁵⁷

The first modern British regulatory "agency" was the Committee on Safety of Drugs ("CSD"), an advisory body that was established in response to the thalidomide disaster in 1961.⁵⁸ Parliament followed up with the Medicines Act of 1968.⁵⁹ Under the new regime, the final decision to approve or reject a new drug was to be made by a national licensing authority with the advice of the Committee on Safety of Medicines ("CSM"),⁶⁰ which essentially replaced the CSD. Pharmaceutical companies were required to apply for approval (called certificates) for clinical trials, and their

⁵⁴ Gesetzes zur Neuordnung des Arzneimittelrechts (Arzneimittelgesetz), v. 24.8.1976 (BGBl. I S.2445) [hereinafter AMG 1976]. Prior to AMG 1976, standards for evaluating safety and efficacy were largely vague, not legally binding, and did not apply to some classes of drugs. AMG 1976 specified criteria to be used in evaluating safety and efficacy, and the Federal Health Ministry ("BGA") promulgated regulations under AMG 1976 specifying required testing regimes. ABRAHAM & LEWIS, *supra* note 27, at 55. Thus AMG 1976 could be said to be the true birth of modern medicines regulation in Germany.

⁵⁵ See ABRAHAM & LEWIS, *supra* note 27, at 73-74 (describing the circumstances surrounding the founding of the Federal Institute for Medicinal Products and Devices ("BfArM")).

⁵⁶ *Id.*; see also Daemrich, *supra* note 50, at 38 (chronicling the effect of the pharmaceutical industry's complaints about the "approval jam" caused by slow approval times).

⁵⁷ ABRAHAM & LEWIS, *supra* note 27, at 74-76. Although BfArM has been said to be warm to industry concerns, it retains an important distinction from its counterparts in other European nations such as Sweden or the U.K. Although BfArM's budget includes substantial revenue from fees, government funds still constitute the majority of the agency's funding. *Id.* at 74.

⁵⁸ *Id.* at 50-51.

⁵⁹ See Medicines Act, 1968, c. 67 (Eng.). The Medicines Act of 1968 remains the primary legislative basis for medicines regulation in the U.K. although large portions of it were superceded by EU measures in 1995.

⁶⁰ See Medicines Act, 1968, c. 67, pt. I, §§ 4(3)(a), 20(4) (Eng.) (providing for the establishment of a committee to give the Licensing Authority "advice with respect to safety, quality or efficacy . . ." and requiring the Licensing Authority to consult this committee before rejecting a drug on those grounds); see also ABRAHAM & LEWIS, *supra* note 27, at 53-54 (describing the role of the CSM).

application for licenses (i.e. marketing authorizations) had to satisfactorily address safety and efficacy issues.⁶¹ However, given the initially permissive nature of regulatory review, the government sought to toughen regulations in the 1970s, even going so far as to review thousands of licenses and recommend the revocation of some of them.⁶² This trend reversed in the 1980s with the election of the Conservative Thatcher government. After instituting an industry-friendly review of regulations, the Thatcher government sacked the de facto Licensing Authority, the Medicines Division of the Department of Health, in 1989 and replaced it with the Medicines Control Agency (“MCA”).⁶³ The pro-industry focus of the MCA was immediately evident. Reduction of review times was a major focus of the new agency, and the MCA sought more consultation with the industry.⁶⁴ Perhaps even more controversial was the move to an entirely fee-based budget; the MCA has been financially self-sufficient since 1991, supporting itself entirely by fees charged to companies seeking MCA review of new products and other MCA services.⁶⁵

Other European nations have had experiences similar to those of Sweden, Germany, and the United Kingdom, namely the establishment and strengthening of national regulation in response to growing concerns about public safety—most notably the thalidomide crisis of 1961—followed by a more recent trend to ameliorate industry concerns over costly, lengthy regulatory review. It is this latter trend that has more significantly shaped the harmonization efforts of the EU.

⁶¹ Medicines Act, 1968, c. 67, § 19 (Eng.).

⁶² See T. B. Binns, *The Committee on Review of Medicines*, 281 BRIT. MED. J. 1614, 1614-15 (1980) (discussing the British government’s review of pharmaceutical licenses begun in 1975).

⁶³ ABRAHAM & LEWIS, *supra* note 27, at 61-63. The Conservative Party (the “Tories”) has historically been known as the pro-business party in the United Kingdom, as opposed to the Labour Party.

⁶⁴ See Peter Marsh, *Scientists Turn Up Volume Control for Pharmaceuticals Tests*, FIN. TIMES, Apr. 25, 1990, § 1, at 8 (examining the Medicines Control Agency’s (“MCA”) focus on accelerating review of new medicines).

⁶⁵ ABRAHAM & LEWIS, *supra* note 27, at 65.

The move to finance pharmaceutical regulation partially or entirely by charging user fees has become increasingly common throughout Europe. It is an important development that is more fully discussed later in Section 3.3. See also discussion *supra* note 49 (discussing Sweden’s usage of fees in medicines regulation).

3.2. *Supranational Regulation in Europe and Harmonization*

Harmonization of regulations within the European zone has been on the European agenda since the 1960s, but the movement remained barely even embryonic until the 1970s. The first measure addressing the regulation of drug development occurred in 1965 with Council Directive 65/65/EEC, which declared that no pharmaceutical drug could be marketed in a Member State unless a marketing authorization was first obtained from that Member State's regulatory authority.⁶⁶ The measure also set out, in general terms, what sort of information applicants needed to provide to obtain an authorization.⁶⁷ This latter aspect of Directive 65/65/EEC was amplified a decade later by Council Directive 75/318/EEC, which laid out in greater detail the standards and protocols applicable to pharmaceutical testing required before applying for authorization.⁶⁸

The Council's very next Directive, 75/319/EEC, represented the most concrete step yet toward harmonization within the European zone. Most importantly, the measure established the CPMP as a central body intended to facilitate harmonization of medicines regulation.⁶⁹ It also provided for the first EU-wide

⁶⁶ Council Directive 65/65/EEC, art. 3, 1965-1966 O.J. SPEC. ED. 24 [hereinafter Directive 65/65/EEC]. This provision, however, hardly represented much of an advancement of harmonization. As discussed in Section 3.1, nations had begun to put modern regulatory systems into place to govern drugs on a national level by this time. Since no European Community body, nor other such body, had ever addressed drug regulation before, Directive 65/65/EEC arguably amounted to a mere recognition of the status quo, or perhaps the mere acknowledgment of developments already well-underway in most European nations.

⁶⁷ *Id.* art. 4. Notably, Directive 65/65/EEC required that results of "physico-chemical, biological or microbiological . . . pharmacological and toxicological tests" as well as results of "clinical trials" be submitted when applying for a nation's marketing authorization. *Id.* Product quality, safety, and efficacy were all named as requirements for marketable drugs. *Id.* art. 5. However, little detail was provided, and a great deal of discretion was clearly left to each national authority.

⁶⁸ Council Directive 75/318/EEC, Annex, 1975 O.J. (L 147) 1 [hereinafter Directive 75/318/EEC]. These provisions considerably fleshed out the requirements for scientific data that were mentioned in Directive 65/65/EEC. *Cf.* Directive 65/65/EEC, *supra* note 66, art. 4.

⁶⁹ Council Directive 75/319/EEC, art. 8, 1975 O.J. (L 147) 13 [hereinafter Directive 75/319/EEC]. Importantly, "the responsibility of [the CPMP] shall be to examine . . . the questions referred to it by a Member State . . ." *Id.* art. 8, § 2 (emphasis added). The focus, then, remained on the impetus of national action, not international action.

approval procedure that was based on mutual recognition of authorizations granted by one Member State's regulatory authority (the "CPMP procedure").⁷⁰

Directive 75/319/EEC envisioned that the CPMP procedure would streamline the approval process for drugs intended for marketing throughout Europe. It provided that once a marketing authorization was obtained in one Member State, the applicant could simultaneously apply for reciprocal approval in five or more additional Member States by requesting that the regulatory authority of the nation of first approval forward copies of the application, via the CPMP, to their counterparts in the other Member States.⁷¹ However, this procedure, the first of its kind in Europe, was very unpopular with the industry and was seldom used.⁷² One reason for this unpopularity was the inability of the applicant company to access the rudimentary dispute resolution mechanism provided in the procedure.⁷³

In response to the failure of the CPMP procedure, a modified version was introduced in 1983 (the "multistate procedure").⁷⁴ The multistate procedure was very similar to its predecessor but had two significant differences: (1) the minimum number of Member States asked to recognize the initial approval was reduced to two, and (2) applicant companies were given direct access to the CPMP if a dispute arose.⁷⁵ Despite these modifications, the pharmaceutical industry still remained wary and failed to utilize the procedure on a large scale.⁷⁶

⁷⁰ *Id.* arts. 9-14.

⁷¹ *Id.* art. 9. Although a central body was forwarding the application, this, in itself, could not be called meaningful harmonization since it was no different than if the applicant company had submitted five additional applications to each of those nations from the beginning.

⁷² See ABRAHAM & LEWIS, *supra* note 27, at 85-86 (discussing the details and results of the "CPMP procedure").

⁷³ See Directive 75/319/EEC, *supra* note 69 art. 12 (providing that the CPMP would hear any dispute brought to it *by a Member State*). If a Member State took exception to another Member State's refusal to recognize its marketing authorization, the CPMP could be consulted by those nations to render a *non-binding* opinion. However, no provisions were made to permit *the applicant company* to access the CPMP.

⁷⁴ Council Directive 83/570/EEC, art. 3, 1983 O.J. (L 332) 1 [hereinafter Directive 83/570/EEC].

⁷⁵ See *id.* (referring to the "holder of the marketing authorization" and providing for direct contact with the CPMP).

⁷⁶ See ABRAHAM & LEWIS, *supra* note 27, at 86-87 (discussing the details and results of the "multistate procedure").

The most significant problem with both the CPMP procedure and the multistate procedure was the inability of an applicant to reliably acquire reciprocal approval from additional Member States based on the approval by the initial reviewing agency.⁷⁷ Given this failure of the mutual recognition principle, these procedures did not offer any real advantage over the traditional method of obtaining individual approvals from each nation separately. Large transnational pharmaceutical companies typically maintained a staff in each target country with expertise in the procedures, laws, and nuances of that country's drug approval process.⁷⁸ Turning instead to a supranational pan-European process neutralized this expertise, and despite the potential cost savings of eliminating these employees, the failure to reliably obtain reciprocal approvals made these procedures very unappealing.

In conjunction with the introduction of the multistate procedure, a separate procedure was instated in 1987 for the approval of certain pharmaceutical products. The so-called "concertation" procedure instituted by Council Directive 87/22/EEC governed certain products defined as "high-technology" products, namely products derived from cutting edge biotechnology.⁷⁹ Like the multistate procedure, the concertation procedure began with an application to a national regulatory authority, called, in this case, the *rapporteur*.⁸⁰ However, unlike

The lowering of the minimum number of Member States from which an applicant was required to seek reciprocal approval in order to utilize the procedure was presumably instituted to try to popularize the use of the procedure. It is interesting to note that despite this reduction, the average number of nations included in such applications actually grew. *Id.* This indicates that pharmaceutical companies were in search of a procedure that would strengthen their ability to win reciprocal approvals in other Member States, a procedure of grander scale rather than the smaller scale of the multistate procedure.

⁷⁷ *Id.*

⁷⁸ *See id.* at 86 ("One of the reasons we might expect industry to welcome mutual recognition is because it allows companies to submit applications without the need for regulatory staff in every country concerned, reducing costs and (possibly) speeding up the approval process.")

⁷⁹ Council Directive 87/22/EEC, 1987 O.J. (L 15) 38 [hereinafter Directive 87/22/EEC]. The types of products encompassed by the concertation procedure included those developed through the use of "recombinant DNA technology, controlled expression of genes coding for biologically active proteins . . . [or] hybridoma and monoclonal antibody methods." *Id.* Annex A. These methods have become increasingly prevalent in biomanufacturing.

⁸⁰ *Id.* art. 3. However, unlike the multistate procedure, regulatory authorities were in some cases *required* to refer applications to the CPMP even if not requested to do so by the applicant company. *See id.* art. 2, § 2 (requiring referral

the multistate procedure, the rapporteur acted essentially as an agent of the EU and not solely on behalf of its national government. Copies of all application materials were to be supplied to the CPMP immediately after their receipt by the rapporteur.⁸¹ The CPMP opinion then acted essentially as a marketing authorization for all Member States concerned.⁸² Member States were then required to seek another CPMP opinion if they wished to deny marketing authorization.⁸³ It is important to note, however, that the CPMP's final opinion was not ultimately binding on Member States under the concertation procedure; a Member State could legally choose to set aside the CPMP opinion in favor of a different national position.⁸⁴

The fate of the concertation procedure was ultimately the same as that of the multistate procedure in that both were eventually replaced. However, the concertation procedure was changed in a less fundamental manner when compared to the substantial reform of the multistate procedure. The obvious reason for this was that the concertation procedure experienced a good deal of success during its lifetime. Marketing authorizations granted by the rapporteur and approved by the CPMP were consistently respected by other Member States, and few cases arose where a Member State refused to abide by the CPMP opinion.⁸⁵

Explaining the success of the concertation procedure as compared to its contemporary, the multistate procedure, offers the first glimpse into what elements are required for successful international harmonization.⁸⁶ The key difference between the two

to the CPMP for some products governed by Directive 87/22/EEC, primarily those developed through the use of genetic manipulation). This signaled the intention of the EU to regulate certain types of technology at least somewhat on a supranational level.

⁸¹ *Id.* art. 3.

⁸² *See id.* art. 2, § 4 (requiring consultation of the CPMP before "withdrawal or . . . suspension of the marketing authorization" if the CPMP had rendered a "favourable opinion on [marketing authorization]"). This essentially indicated that a favorable CPMP opinion amounted to an effective authorization that then had to be withdrawn or suspended in order to prevent the product from being sold.

⁸³ *Id.*

⁸⁴ Directive 87/22/EEC only requires that if a Member State wishes to deny marketing approval despite a second favorable CPMP opinion, it must notify the CPMP of its decision to do so within thirty days. *Id.* art. 4, § 4.

⁸⁵ ABRAHAM & LEWIS, *supra* note 27, at 97.

⁸⁶ It could alternatively be argued that the disparity in success was not due to any characteristic of either procedure but rather differences in the types of

is the level of centralization, particularly the level of involvement by the CPMP. The multistate procedure effectively operated independent of the CPMP. A company seeking marketing authorization for a drug would apply to a national regulatory authority acting purely on behalf of its national government alone. If an authorization was granted, two or more other national agencies were asked to recognize the first nation's authorization, which was granted in a review process they were not originally privy to. The decision to recognize the first nation's authorization was left to the reviewing nation's discretion. This process enabled the reviewing nation to consider its own national priorities in deciding whether or not to recognize another country's authorization. The CPMP only became involved in the event of a dispute; the applicant company could petition for the CPMP to intervene. However, the CPMP had no authority to forcefully perturb any Member State's national regulatory authority.⁸⁷

In contrast, the concertation procedure was a far more centralized process. The rapporteur acted on behalf of the entire EU. Every concerned Member State's regulators were involved in the approval process via the CPMP. Any objections were discussed at the level of the CPMP *prior* to any grant of marketing authorization. This *collective* process culminated in an opinion promulgated by the CPMP, albeit ultimately non-binding.

The importance of centralization was recognized in 1993 as the EU took the next step toward true harmonization across the European zone. The multistate and concertation procedures were revamped to become the decentralized and centralized procedures

products governed by each. However, nothing inherent in the nature of the products governed by the concertation procedure indicates that they would present lesser concerns of safety, efficacy, or quality as compared to products governed by the multistate procedure. In fact, given that many of the concertation procedure products were highly innovative, they could be said to pose greater potential risks given the relative lack of experience with such technology. Political and economic concerns would also be just as, if not more likely, to trigger resistance for the products governed by the concertation procedure given the controversial nature of many new biotechnologies such as genetic engineering.

⁸⁷ Member States legally had to give "due consideration" to the marketing authorization issued by another Member State. Directive 83/570/EEC, *supra* note 74, art. 3. However, this certainly fell well short of requiring mutual recognition or providing the CPMP with any effective legal grounds or authority to force Member States to capitulate. In fact, the only requirement made of Member States when faced with an adverse CPMP opinion was to notify the CPMP within sixty days of their decision whether or not to abide by the opinion. *Id.*

respectively.⁸⁸ In addition, a new EU-level agency, the EMEA, was established with the CPMP as its scientific arm.⁸⁹ Lastly, stricter guidelines governing the timetable for reviewing applications were instituted, a move roughly concurrent with similar changes in Europe's major national regulatory agencies.⁹⁰

The centralized procedure, the technical successor to the concertation procedure, has two important new features. First, applications are no longer made to a national regulatory agency acting as rapporteur but are instead submitted directly to the EMEA.⁹¹ Second, and more importantly, the EMEA/CPMP's final decision regarding an application is now binding on all Member States.⁹² The EMEA/CPMP has thus become the ultimate regulatory authority for the entire EU with respect to applications under the centralized procedure. Still, while this change is not an unimportant one, its significance is somewhat muted in that the CPMP for all practical purposes held this role under the concertation procedure in effect if not in name.⁹³

In contrast, the decentralized procedure is markedly different

⁸⁸ See Council Directive 93/39/EEC, 1993 O.J. (L 214) 22 (amending the multistate procedure to create the new decentralized procedure); Council Regulation 2309/93, 1993 O.J. (L 214) 1 (replacing the concertation procedure with the centralized procedure).

The term *decentralized procedure* is a descriptive term (like the previously introduced terms *CPMP procedure*, *multistate procedure*, and *concertation procedure*) adopted for the purposes of this Comment due to its value in distinguishing its characteristics from the centralized procedure. The decentralized procedure, however, is actually a *more centralized* version of its immediate predecessor, the multistate procedure. Along with the term *mutual recognition procedure*, which refers to the decentralized procedure, these are the common labels used in scholarship. See, e.g., ABRAHAM & LEWIS, *supra* note 27, at 88, 97 (utilizing these terms).

⁸⁹ Council Regulation 2309/93, *supra* note 88, tit. 4.

⁹⁰ See Council Directive 93/39/EEC, *supra* note 88, art. 3, § 1 (setting strict time limits for the decentralized procedure); Council Regulation 2309/93, *supra* note 88, tit. 2, ch. 1 (setting strict time limits for the centralized procedure, including a 210 day limit for issuance of the CPMP opinion after receipt of an application); cf. *supra* Section 3.1 (discussing the recent trend of European agencies reducing review times).

⁹¹ See Council Regulation 2309/93, *supra* note 88, tit. 1, art. 4, § 1 ("In order to obtain the authorization . . . [the applicant] shall submit an application to the European Agency for the Evaluation of Medicinal Products ["EMEA"] . . .").

⁹² *Id.* tit. 2, art. 12, §§ 1-2. In fact, the decision is binding on all Member States, not just those specifically targeted by the applicant, even if the applicant does not intend to sell the product in all Member States.

⁹³ See discussion, *supra* pp. 172-74 (describing the concertation procedure).

from its nominal predecessor, the multistate procedure. The basic mechanism for action is the same; companies must still first apply for and obtain a marketing authorization in one Member State.⁹⁴ The applicant then requests mutual recognition of that authorization from additional countries and forwards the original application sent to the nation of first approval to other Member States along with a copy of the authorization.⁹⁵ However, should a Member State refuse reciprocal approval and the disagreement cannot be resolved via negotiation, the matter is referred for arbitration before the CPMP.⁹⁶ More importantly, the decision of the CPMP is binding on the Member States involved.⁹⁷

The magnitude of this change should not be underestimated. Practically speaking, the result of the decentralized procedure has been the near eradication of disputes regarding mutual recognition as measured by referrals for CPMP arbitration.⁹⁸ The pressure for Member States to conform and recognize the marketing authorizations of other Member States is enormous and comes from several sources.

First, due to strict time limits prescribed for each phase of the process, regulators are hard-pressed to gather the materials necessary to adequately support a decision to reject an application for mutual recognition.⁹⁹

Second, the prospect of an adverse CPMP decision acts as a deterrent. No national regulatory agency savors the possibility of its authority being overruled by a binding CPMP decision.

Lastly, and perhaps most importantly, the new European

⁹⁴ Council Directive 93/39/EEC, *supra* note 88, art. 3, § 1 (revising, *inter alia*, Article 9 of Directive 75/319/EEC).

⁹⁵ *Id.*

⁹⁶ *Id.* (revising Article 10 of Directive 75/319/EEC). Member States involved in the dispute and the applicant company "shall use their best endeavours to reach agreement" *Id.* If those negotiations fail, however, arbitration is mandatory. *Id.*

⁹⁷ Each Member State concerned is now required to conform with the decision of their regulatory authority with that of the CPMP within thirty days of adoption by the European Commission. *Id.*

⁹⁸ As of 2002, arbitration referrals arising out of the mutual recognition procedure have never numbered in the double digits in any given year, with a peak of nine in 2002 to bring the total to thirty-two since the procedure's inception. See EMEA, EIGHTH ANNUAL REPORT § 2.5 (2002) at 16-17 and accompanying tbl. (marking an increase in arbitration referrals in 2002), available at <http://www.emea.eu.int/pdfs/general/direct/emeaar/005502en.pdf>.

⁹⁹ ABRAHAM & LEWIS, *supra* note 27, at 91.

regulatory regime encourages an atmosphere of competition among agencies. Pharmaceutical companies understandably choose a nation of first approval very carefully. It is obviously in their best interest to select an agency that is most likely to approve their drugs as quickly and efficiently as possible. In addition, they are unlikely to select an agency that refused to grant reciprocal approval in a previous application for mutual recognition. Given that virtually all European agencies in medicines regulation now depend to some degree on fees collected from pharmaceutical companies, the financial pressure to attract as many applicants as possible is extremely high.¹⁰⁰

3.3. *Lessons of the European Harmonization Effort*

Several salient points emerge from the examination of European harmonization efforts to date. First and foremost, the influence of the pharmaceutical industry has been enormous and omnipresent. The current trend in national medicines regulation in Europe is reform favoring the interests of the industry, most notably in the form of reducing the length of drug review times and increasing consultations with the industry.

Furthermore, industry influence is unlikely to wane for the foreseeable future since it is being built into the structure of national medicines regulation. The MCA is not the only agency supported wholly, or in part, by industry user fees. The MPA is also entirely supported by industry fees,¹⁰¹ and even historically reluctant German regulators now supplement the BfArM budget with user fees.¹⁰²

The influence of industry has been powerful in the development of supranational regulation in Europe as well. In fact, the replacement of the multistate procedure (and concertation procedure) came upon the heels of a series of recommendations issued by the Association of the British Pharmaceutical Industry ("ABPI") in 1988.¹⁰³ Virtually all of the reforms recommended by

¹⁰⁰ See discussion *infra* Section 3.3.

¹⁰¹ SWEDISH MEDICAL PRODUCTS AGENCY, MAKING LIFE A LITTLE SAFER 1 (n.d.), available at http://www.mpa.se/eng/about_mpa/MPA_pres_en.pdf (last updated Jan. 10, 2002).

¹⁰² See ABRAHAM & LEWIS, *supra* note 27, at 74 (discussing the partially fee-based budget and retention of substantial government funding by the BfArM). The BfArM is notable in that it retains substantial government funding. *Id.*

¹⁰³ See *id.*, at 87-88 (detailing the recommendations set out by the Association of the British Pharmaceutical Industry ("ABPI") for the improvement of European

the ABPI were eventually enacted when the decentralized and centralized procedures were installed. Therefore, it can be said that the push for harmonization was effectively—and successfully—instigated by industry.

Another key lesson of the European experience has been the importance of strong centralization. The failure of the multistate procedure (and the CPMP procedure before that) and the subsequent success of the decentralized and centralized procedures convincingly demonstrates the need for a powerful, central organizing force in order to prevent national interests from derailing harmonization. The converse is an important lesson as well; without a meaningful central authority, divergent national interests will eventually thwart harmonization efforts. This maxim proved true in Europe and would be an even greater danger to efforts at harmonizing regulations between more dissimilar nations.

4. COMPARING THE ICH TO THE EUROPEAN EXPERIENCE

Even within its brief history, the ICH has shown considerable promise in making international harmonization a reality. However, despite the optimism in these early stages, an examination of its work to date portends upcoming conflicts. The parallels to the European experience are significant, and unique factors brought into play by the involvement of the United States and Japan will also enlarge obstacles to progress.

One crucial similarity with European harmonization is obvious from a superficial glance at the organization of the ICH. The parties to the ICH include the regulatory agencies of the three participating nations,¹⁰⁴ as well as the *major associations of each nation's pharmaceutical industry*.¹⁰⁵ In addition, the ICH Secretariat is run by the International Federation of Pharmaceutical Manufacturers Associations ("IFPMA").¹⁰⁶ The influence of

harmonization efforts).

¹⁰⁴ These are the U.S. FDA, the European Commission (namely, the EMEA), and the Japanese Ministry of Health, Labor and Welfare ("MHLW"). ICH GLOBAL COOPERATION GROUP, ICH INFORMATION BROCHURE 6-8 (2001). Each agency's scientific arm is thus also involved: CDER/CBER, the CPMP, and the Japanese National Institute of Health Sciences ("NIHS").

¹⁰⁵ These are PhRMA from the United States, the European Federation of Pharmaceutical Industries and Associations ("EFPIA"), and the Japan Pharmaceutical Manufacturers Association ("JPMA"). *Id.*

¹⁰⁶ *Id.* at 8.

industry concerns could not be more plain, and a closer analysis of the ICH's output to date only reinforces this connection.

4.1. A Brief History of the ICH

The ICH was formed in Brussels, Belgium, at a meeting of the interested parties hosted by the European Federation of Pharmaceutical Industries and Associations ("EFPIA") in April of 1990.¹⁰⁷ A Steering Committee was formed as well as Expert Working Groups ("EWGs") assigned to specific "Topics."¹⁰⁸ These Topics were subdivided into three categories: Quality, Safety, and Efficacy.¹⁰⁹ Each Topic was, and continues to be, subject to a five-step process concluding with implementation in each of the three zones.¹¹⁰ Both the Steering Committee and the EWGs meet twice a year at a location rotating between the three participating nations.¹¹¹ In addition, a full ICH Conference is held every two years and is attended by thousands of representatives of the six parties as well as those of other interested parties; the most recent conference was ICH6 held in Osaka, Japan in 2003.¹¹²

The accomplishments of the ICH have been impressive. Nearly sixty ICH Topics have become official Guidelines and reached the implementation stage as of 2003, meaning a harmonized text has

¹⁰⁷ *Id.* at 4.

¹⁰⁸ *Id.* at 4-5. This remains the mechanism through which the ICH operates. A proposed Topic is first reviewed by the Steering Committee, then referred to an EWG to work out the technical details. *Id.* at 14-16. The EWG reports back to the Steering Committee periodically, and with its final recommendation, the Steering Committee determines whether it should move forward to implementation. *Id.* at 16-17.

¹⁰⁹ ICH, ICH Guidelines, at http://www.ich.org/TxtServer.jsr?@_ID=250&@_TEMPLATE=272 (last visited Feb. 22, 2005). A fourth category of Topics, termed "Multidisciplinary" Topics, was formed to cover subject matter not well suited for the original three categories. *See id.* (explaining that "Multidisciplinary Topics" are "cross-cutting Topics which do not fit uniquely into one of the above [three] categories.").

¹¹⁰ *See* ICH GLOBAL COOPERATION GROUP, *supra* note 104, at 14-18 (explaining the five-step process for ICH Topics). The goal of the process is the formulation of a harmonized text that is agreed upon by all of the parties. Theoretically, the final step of implementation should be more or less a formality since each participating regulatory agency has already agreed to the provisions of the harmonized text by that point. However, as we shall see, implementation may not be quite so simple if a politically or culturally sensitive subject is involved.

¹¹¹ *Id.* at 4.

¹¹² The previous five conferences were: ICH1 in Brussels (1991), ICH2 in Orlando (1993), ICH3 in Yokohama (1995), ICH4 in Brussels (1997), and ICH5 in San Diego (2000). *Id.* at 10.

been approved by all parties, including all three regulatory agencies.¹¹³ Many of these Guidelines pertain to uncontroversial matters in which much international agreement already existed.¹¹⁴ However, some represent meaningful progress in achieving harmonization.

One simple example concerns the requirement of toxicity testing. The Centre for Medicines Research ("CMR"), a U.K. based group backed by the ABPI that has participated as an observer, clashed with the FDA on the length of toxicity testing to be required for marketing approval. The CMR argued that the European standard of six months was adequate while the FDA stood by its requirement of twelve months.¹¹⁵ After deliberation and study by the ICH, the parties were able to compromise on a harmonized Guideline that allowed for six month studies in rodents and nine month studies in non-rodents.¹¹⁶

Perhaps the most significant new achievement of the ICH has been the adoption of the Common Technical Document ("CTD"), which is intended to serve as an acceptable alternate form for drug marketing approval applications in all three jurisdictions.¹¹⁷ Portions of the CTD have reached implementation in one or more zones.¹¹⁸ The long-term implications of the CTD merit closer analysis as they begin to reveal the obstacles awaiting the ICH.

¹¹³ *Id.* app. 3, at 26-28.

¹¹⁴ See, e.g., *Guideline on the Need for Carcinogenicity Studies of Pharmaceuticals*, ICH Steering Committee, ICH Guideline S1A, at 2 (Nov. 29, 1995) (describing the historical background of the Guideline and the similarity amongst the parties' previous requirements), available at <http://www.emea.eu.int/pdfs/human/ich/014095en.pdf>.

¹¹⁵ See ABRAHAM & LEWIS, *supra* note 27, at 137-38 (recounting the toxicity testing debate between the Centre for Medicines Research ("CMR") and the FDA). Although a matter of a few months may not seem significant to the layperson, the fastidiousness with which the FDA refused to alter its stance suggests this was not a trivial issue.

¹¹⁶ See *Duration of Chronic Toxicity Testing in Animals: Rodent and Non-Rodent Toxicity Testing*, ICH Steering Committee, ICH Guideline S4, at 2 (Sept. 2, 1998).

¹¹⁷ *Organisation of the Common Technical Document for the Registration of Pharmaceuticals for Human Use*, ICH Steering Committee, ICH Guideline M4, at 1 (Nov. 8, 2000) [hereinafter *CTD Organization*].

¹¹⁸ See *Status of the Common Technical Document Guidelines*, at http://www.ich.org/UrlGrpServer.jsr?@_ID=1325&@_TEMPLATE=272 (last updated Feb. 18, 2005) (listing the status of implementation efforts of the various CTD guidelines).

4.2. *The Common Technical Document*

The potential of the CTD in assisting harmonization efforts is palpable. Cooperation between agencies would be aided if they all received the necessary information organized in the same way. More importantly, adoption of the CTD indicates a willingness of all three agencies to: (1) require a common set of information for marketing approval, (2) accept clinical research data from trials performed on foreign soil, and (3) move toward some level of mutual recognition.

The first of these possibilities is the most tangible at present. While it is permitted for each agency to require additional individualized documents—indeed, the first module of the CTD explicitly calls for some degree of individualization¹¹⁹—too much deviation from the common form would ultimately defeat the entire purpose of the CTD. If the CTD is to succeed, all three agencies must commit to accepting basically the same set of information. The critical benefit this presents to industry is a more efficient and economical application process. Rather than generating multiple different application forms, each of which consists of hundreds of thousands of pages, a company need only generate one document.

Acceptance of clinical research data from trials performed abroad is a more dramatic leap from traditional practice. However, it is a measure vital to accomplishing one of the ICH's stated mission objectives, the elimination of unnecessary duplicative clinical trials.¹²⁰ Other ICH Guidelines have also broached the subject.¹²¹ Together with the CTD, these Guidelines reflect an overall commitment within the ICH to achieve harmonization in this area. Indeed, implementation of this objective in the three ICH zones has already begun in earnest.¹²²

¹¹⁹ See *CTD Organization*, *supra* note 117, at 2 (“Module 1 is region specific.”). Module 1 consists primarily of administrative information.

¹²⁰ See ICH GLOBAL COOPERATION GROUP, *supra* note 104, at 23 (stating the ICH's objective to promote “more economical use of human . . . resources . . .”); *cf. supra* Section 2.4 (discussing the elimination of duplicative clinical trials as a rationale for international harmonization).

¹²¹ See, e.g., *Ethnic Factors in the Acceptability of Foreign Clinical Data*, ICH Steering Committee, ICH Guideline E5, at 1 (Feb. 5, 1998) (stating as an objective, “minimizing duplication of clinical studies”).

¹²² See ICH, *Efficacy Guidelines* (listing the status of implementation efforts of the various Efficacy Guidelines), at http://www.ich.org/UrlGrpServer.jserv?_ID=475&_TEMPLATE=272 (last visited Feb. 22, 2005).

Furthermore, industry stands to benefit tremendously yet again. Pharmaceutical companies will only need to conduct one series of costly clinical trials per drug rather than an additional series for each jurisdiction.

Mutual recognition would seem a logical next step. Assuming the CTD effort achieves its goals, all three jurisdictions would be using an essentially identical form and making assessments based on identical data. The ICH has also worked to harmonize the scientific requirements for marketing authorizations.¹²³ Although the ICH has never explicitly declared mutual recognition to be a goal, evidence for such a direction can be inferred from numerous sources. The CTD effort itself can be interpreted to be an action in furtherance of eventual mutual recognition.

Certainly the three parties representing the industry would welcome such a move as they did in Europe. However, any proposed mutual recognition regime must be a strong one because a weak regime without strong central organization is bound to fail as it did in Europe. Unfortunately, a number of factors complicate the installation of a strong mutual recognition regime in the ICH context.

4.3. *Unique Difficulties Faced by the ICH Initiative*

As seen in Europe, centralization is critical to the success of mutual recognition. Unfortunately, disparities in national interests between the participating nations of the ICH are in many ways much larger than those found in Europe. First and foremost, EU nations were already heavily invested in broad-scale integration of their legal, economic, and political systems through the EU. This joint enterprise mitigates both desires to maintain national sovereignty and conflicts between national interests. The United States and Japan obviously are not as closely linked to each other or to Europe. Thus, the importance of particular national interests and the need for maintenance of national sovereignty are likely to be more of a factor in the ICH than they were within the EU.

While the FDA, EMEA/CPMP, and MHLW have largely proven themselves to be non-partisan agencies, the magnitude of a

¹²³ Since all finalized Guidelines issued by the ICH Steering Committee are texts agreed to by all of the parties, the bulk of the Quality, Safety, and Efficacy Guidelines represent strides taken in harmonizing scientific requirements. For a list of these Guidelines, see ICH GLOBAL COOPERATION GROUP, *supra* note 104, at 26-28.

decision to adopt mutual recognition will almost certainly pique the interests of at least some of their political overseers. Certain specific cases are obvious causes for concern. The controversy in the United States over the abortion debate and its questionably linked offspring, the stem cell debate, will almost certainly cause consternation at the FDA as it attempts to harmonize with Europe and Japan. Another potential battleground is the current shouting match over the use of genetically modified organisms (“GMOs”), technology the United States has embraced but Europe opposes. Each one is examined in turn with an eye toward the ICH and harmonization in general.

4.3.1. *The United States “Culture of Life” and Harmonization*

The abortion debate in the United States continues to rage decades after the landmark decisions in *Roe v. Wade*¹²⁴ and *Planned Parenthood v. Casey*¹²⁵ extended constitutional protection to abortion rights. As recently as in 2003, Congress has passed legislation restricting abortion rights, legislation signed by President George W. Bush on November 5 of that year.¹²⁶ President Bush, a conservative Republican, has also promulgated a series of Executive Orders and administrative actions that are seen as limiting abortion rights.¹²⁷ Clearly, the atmosphere in the United

¹²⁴ See generally *Roe v. Wade*, 410 U.S. 113 (1973) (holding that the U.S. Constitution’s protections of individual privacy extend to a woman’s right to an abortion, although in late stages of pregnancy this right is balanced out by a compelling state interest in protecting unborn children). The Roe Court proposed a trimester scheme in which a woman’s constitutional right to an abortion would be tempered by some acceptable regulation by states in the latter trimesters. *Id.* at 145-49.

¹²⁵ See generally *Planned Parenthood v. Casey*, 505 U.S. 833 (1992) (holding that any measure that placed an “undue burden” on a woman’s right to an abortion is unconstitutional, rejecting the trimester scheme proposed under *Roe v. Wade*).

¹²⁶ Partial-Birth Abortion Ban Act, 18 U.S.C. § 1531 (2003). The Act renders the performance of partial-birth abortions a federal crime punishable by up to two years in prison. *Id.* § 1531(a). This legislation has been predictably challenged in court and is certain to be granted Supreme Court review. A similar state law in Nebraska was struck down in 2000 by the Supreme Court. See *Stenberg v. Carhart*, 530 U.S. 914 (2000) (holding that Nebraska’s partial-birth abortion ban was unconstitutional because it lacked an exception for cases in which the life of the mother was threatened). However, proponents of the federal ban are more hopeful since it provides that the ban “does not apply to a partial-birth abortion that is necessary to save the life of a mother” 18 U.S.C. § 1531(a).

¹²⁷ In fact, one of his very first actions as President after narrowly winning

States for the sale of abortion drugs and related pharmaceutical products is all but assured.

Attitudes in Europe toward abortion, though not uniform either, are quite different from that of Americans. The differences between Europe and the United States on this issue are exemplified in the ongoing debate over RU-486, an oral abortion drug developed in Europe and approved by the FDA in 2000.¹²⁸ In late 2003, emboldened by the replacement of the pro-choice Clinton Administration with the pro-life Bush Administration, Republican Congressmen Jim DeMint and Roscoe Bartlett introduced a bill to suspend RU-486's marketing authorization.¹²⁹ In contrast, the drug has been approved in much of Europe for over a decade and has yet to see a significant challenge.

The stated basis for the DeMint-Bartlett bill is safety concerns raised by the deaths of two American women that took RU-486.¹³⁰ However, many pro-choice groups accuse them and President Bush of using these few deaths as an excuse to pursue an unrelated political agenda, namely undermining abortion rights.¹³¹ The circumstances surrounding RU-486's initial approval also show marks of political involvement.¹³²

The abortion debate has also spawned a firestorm in the United States over stem cell research. In August of 2001, President Bush

the 2000 election was the reimposition of the so-called global gag rule, which bans federal funding for international groups that actively push abortion as a tool for family planning. Robin Toner, *The New Administration: The Abortion Issue*, N.Y. TIMES, Jan. 22, 2001, at A16. President Bush announced it as the first step in his fight to create a "culture of life" in the United States. *Id.*

¹²⁸ See Marc Kaufman, *FDA Approves Abortion Pill: Family Planning Groups Hail 'Milestone'*, WASH. POST, Sept. 29, 2000, at A1 (reporting the FDA's approval of RU-486 and the reactions of both supporters and opponents).

¹²⁹ RU-486 Suspension and Review Act, H.R. 3453, 108th Cong. (2003). A version is before the Senate as well. S. 1930, 108th Cong. (2003).

¹³⁰ See Jeremy Manier, *Teen's Death Rekindles Abortion Pill Battle*, CHI. TRIB., Nov. 30, 2003, at C14 (discussing the death of Holly Patterson and its role in sparking the movement in Congress to revoke RU-486's marketing authorization).

¹³¹ See *id.* (reporting skepticism as to the motives behind the movement to fight RU-486). These accusations are bolstered by comparable or more severe fatality statistics for uncontroversial drugs. For example, 130 men died taking Viagra in the eight months following its approval, a result that did not spark calls for its withdrawal. *Id.*

¹³² See Sharon Bernstein, *Persistence Brought Abortion Pill to U.S.*, L.A. TIMES, Nov. 5, 2000, at A1 (relating the lengthy, convoluted road that RU-486 took to FDA approval and the possible involvement of the Clinton White House in easing its passage).

used one of his first primetime television appearances to address the prickly issue of federal funding for embryonic stem cell research.¹³³ The link to abortion is that the original sources of embryonic stem cells are human embryos, and harvesting the cells terminates the embryos, which some pro-life advocates equate with murder.¹³⁴ President Bush did not seek to ban federal funding altogether, but imposed tight restrictions that would end the practice of embryonic stem cell harvesting.¹³⁵

Unlike abortion, which ultimately touches on only a handful of pharmaceutical products, stem cell research is often heralded as the most exciting avenue of new therapy research in the twenty-first century. President Bush's present policy only concerns the federal funding of stem cell research. However, a wild stretch of the imagination is not required to picture a conservative administration or a conservative-controlled Congress injecting itself into new drug approvals in the same way Congressmen DeMint and Bartlett are attempting to do with RU-486.

These events lend little confidence that politically sensitive issues like abortion or stem cell research will not affect the behavior of American regulators and lawmakers. For example, if an ICH mutual recognition system existed and a stem cell-based drug approved in Europe sought reciprocal approval in the United States, enormous political pressure could be applied to have it rejected. It is an inauspicious sign indeed for the ICH if the success of mutual recognition is dependent on which political party is in control of the White House and/or Congress. Such uncertainty would undoubtedly make a pharmaceutical company think twice before pursuing mutual recognition, especially considering the

¹³³ Marc Sandalow, *Bush Approves Strict Rules for Stem Cell Funding*, S.F. CHRON., Aug. 10, 2001, at A1.

¹³⁴ See *id.* ("Members of the religious right, some of whom had equated stem cell research to murder, were divided on the president's approach."); see also Frank Bruni, *Bush Gives His Backing for Limited Research on Existing Stem Cells*, N.Y. TIMES, Aug. 10, 2001, at A1 (describing how President Bush's decision is keeping him from "breaking a campaign pledge not to finance the destruction of what he called live embryos").

¹³⁵ Existing embryonic stem cell lines can be replicated indefinitely, but President Bush's policy bans federal funding for research involving the gathering of new stem cell lines from human embryos, even from embryos that would otherwise be discarded in, for example, the process of *in vitro* fertilization. See Bruni, *supra* note 134, at A1 ("[President Bush] talked of the 'frozen embryos' in fertility clinics But [he] did not ultimately permit federal financing of that.").

public relations issues.¹³⁶

4.3.2. *Europe and the GMO Debate*

In addition to the United States, other nations are being affected by political concerns over biotechnology. For over a decade now, the arguments have raged across the Atlantic over the use of GMOs in agriculture. The FDA does not distinguish between genetically modified crops—such as those transformed to be resistant to certain pests—and crops that have never been modified by biotechnology.¹³⁷ In fact, the full extent of genetic modification in U.S. agriculture is essentially unknown since there is no way to differentiate between GMO and non-GMO crops.¹³⁸

Unlike the United States, European nations have reacted quite viscerally against the use of GMOs. Aside from the public uproar raised by various advocacy groups,¹³⁹ the impact of this difference of opinion is evident in the chilling effect it has had on U.S.-Europe trade in agricultural products.¹⁴⁰ Since U.S. food exports, for example, are not labeled as having or not having been genetically modified, the European reaction has been to avoid U.S. agricultural products altogether.¹⁴¹ If this trend continues, the damage to the U.S. agriculture industry will be substantial.

While the GMO controversy has not to date spilled over into the realm of pharmaceutical products, the potential certainly exists. As mentioned earlier, genetic technology is becoming increasingly prevalent in the pharmaceutical industry.¹⁴² Among the genetic technologies frequently used is the genetic modification of animal

¹³⁶ See Bernstein, *supra* note 132, at A24 (depicting the reluctance of manufacturers to pursue FDA approval of RU-486 due to political and public relations issues).

¹³⁷ For an in-depth discussion of the GMO debate and its underpinnings, see, for example, Kim Brooks, *History, Change and Policy: Factors Leading to Current Opposition to Food Biotechnology*, 5 GEO. PUB. POL'Y REV. 153 (2000), and George E.C. York, *Global Foods, Local Tastes and Biotechnology: The New Legal Architecture of International Agriculture Trade*, 7 COLUM. J. EUR. L. 423 (2001).

¹³⁸ See Brooks, *supra* note 137, at 154 (noting Europe's opposition to genetically modified crops).

¹³⁹ See, e.g., Lim Li Ching, Institute of Science in Society, *Keeping Europe GM-Free*, May 12, 2003, available at <http://www.i-sis.org.uk/KEGMF.php>.

¹⁴⁰ See York, *supra* note 137, at 427-28 (describing the steep declines in U.S. agricultural exports to Europe following the GMO furor in the 1990s).

¹⁴¹ Brooks, *supra* note 137, at 154.

¹⁴² See *supra* note 79 and accompanying text.

cells to induce them to produce certain compounds.¹⁴³ While this phenomenon has perhaps not been fully studied, the genetic manipulation of animals raises many of the same concerns as that of plants, particularly the ecological and long-term medical impacts of such manipulation.¹⁴⁴ It may just be a matter of time before attention shifts to the use of biotechnology in pharmaceutical development, as it has in the United States.

The EU is currently reviewing measures that would, among other things, require labeling of GMO products and impose other restrictions on the ability of U.S. food manufacturers to sell their goods in Europe.¹⁴⁵ If this sort of approach was applied to what European consumers considered to be objectionable pharmaceutical products, the success of the mutual recognition principle as it applied to GMO-based products from the United States and Japan would be in grave peril.

4.3.3. *The Potential Hazard of Politics*

The danger of these controversies with regard to the ICH is that political sensitivities, which are more pronounced across oceans than within Europe, could lead to each Party reserving the right to enact measures against particular pharmaceutical products based on political concerns rather than issues of quality, safety, or efficacy. However, such a scheme would be sure to fail due to industry disapproval. Given the uncertainty of politics, industry is likely to be uninterested in using a procedure vulnerable to political whims, thus resulting in a failure much like that suffered by the CPMP and multistate procedures in Europe.¹⁴⁶

¹⁴³ See, e.g., Brandon Price & Stephanie Finnegan, *Biomanufacturing Strategies: Protein-Production Planning in a Resource-Constrained Environment*, CONTRACT PHARMA, Nov. 2000, available at <http://www.contractpharma.com/nov001.htm> (discussing the use of genetic technology in pharmaceutical manufacturing).

¹⁴⁴ See York, *supra* note 137, at 433 (describing the concerns that GMOs may have negative long-term effects on human health, such as unintended allergic or toxic effects, and on ecosystems).

¹⁴⁵ For a discussion of some of these proposals and their potential impact on U.S.-Europe relations vis-à-vis the WTO, see Joanne Scott, *European Regulation of GMOs and the WTO*, 9 COLUM. J. EUR. L. 213 (2003).

¹⁴⁶ After all, the traditional approach of obtaining individual approvals in each zone would remain available. The lesson of the European experience was that pharmaceutical companies are reluctant to substantially revamp their operating procedures without confidence in the reliability of the alternative harmonized procedure. See discussion *supra* Section 3.2. (suggesting lack of reliability as the reason pharmaceutical companies did not adopt the CPMP and

Unfortunately, it is difficult to imagine the United States permitting Europe to set any de facto American regulatory policy pertaining to abortion or even stem cell research. Likewise, the EU is likely to resist American fiat on GMO-based products as it has been for a decade with regard to agricultural products. The involvement of Japan further complicates the picture as a third nation with national interests that have historically been even more unique and different.

5. KEY CONSIDERATIONS FOR THE FUTURE OF THE ICH

The key conflict that the ICH is likely to face is that between industry concerns and national interests. As discussed above, the ICH is, to a significant extent, beholden to industry interests.¹⁴⁷ This is very similar to European harmonization efforts, which resulted in the current highly centralized, industry-friendly system.¹⁴⁸ However, the ICH faces more significant obstacles to centralization than the EU system.¹⁴⁹ So can these obstacles be overcome?

The European experience made clear the consequences of a weak, decentralized regulatory regime. Industry will not make use of a system of mutual recognition without reliable rates of reciprocal approval.¹⁵⁰ Without centralization, reliability is uncertain if not unlikely based on the dismal failures of the CPMF and multistate procedures in Europe. Therefore, the ICH must adopt guidelines favoring accountability and centralization in the model of the European system if mutual recognition is to succeed.

Given that the ICH has yet to embrace mutual recognition as a goal, one might wonder whether it even needs to traverse such potentially contentious ground to be a success. However, without mutual recognition, the ultimate worth of the ICH is limited, perhaps even marginal. The pharmaceutical industry, having experienced the benefits of mutual recognition in Europe, will continue to espouse it as a priority and will not be satisfied with

multistate procedures).

¹⁴⁷ See discussion *supra* Section 3.3 (noting the influence of the industry).

¹⁴⁸ See discussion *supra* Section 3.2 (describing the evolution of European drug regulations harmonization).

¹⁴⁹ See discussion *supra* Section 4.3 (discussing the difficulties facing the ICH that did not arise during European harmonization efforts).

¹⁵⁰ See discussion *supra* Section 3.2-3 (examining the motivations and goals of the industry with regard to drug regulations harmonization).

what currently amounts to harmonization of administrative minutiae as compared to the momentous reform represented by mutual recognition. The commitment of the industry in winning an effective mutual recognition regime was evident in Europe. Given the industry's influence on the ICH and on medicines regulation in general, a reckoning over the issue is probably unavoidable whether it comes during or after the lifetime of the ICH project.

Is sufficient centralization of pharmaceutical regulation possible then under the auspices of the ICH? Is the ICH effort doomed to fail due to insurmountable obstacles? Unfortunately this is a real possibility, at least given the current state of world affairs. As already noted, the national interests of the three parties may not be fully compatible with a strong central regulatory regime modeled after that of Europe.¹⁵¹

However, the political power of the industry should not be discounted. Although the impediments to harmonization in the ICH context are greater than those that faced the EU, reasons certainly exist to believe that industry concerns are up to the task of overcoming these challenges.

In the United States, the FDA budget has been partially comprised by industry user fees since the passage of the Prescription Drug User Fee Act ("PDUFA") in 1992.¹⁵² Although the proportion of the FDA's funding made up of user fees is currently relatively small, the legal framework for potentially greater FDA ties to the industry was established by PDUFA. In addition, the pharmaceutical industry remains one of the most powerful lobbies in the United States.¹⁵³

In sum, in order for the ICH to truly fulfill its potential, all three regulatory agencies – the FDA, the EMEA, and the MHLW – must be willing to subordinate individual political sensitivities to the greater purpose of international harmonization. A strongly centralized mutual recognition regime is an essential component for successful international harmonization, and all parties to the ICH must accept that fact. Although current circumstances perhaps make this development premature, some cause for

¹⁵¹ See discussion *supra* Section 4.3 (describing examples of large disparities in national interests).

¹⁵² 21 U.S.C. § 379g-h (1992).

¹⁵³ See discussion *supra* note 17 (assessing the strength of the U.S. industry lobby in healthcare).

optimism exists in the continuing strength of the industry lobby, which has shown itself to be sufficiently potent to push forward harmonization efforts to date.

6. CONCLUSION

The ICH is a truly exciting step forward in the harmonization movement. The global scale of the pharmaceutical and health care industries makes international harmonization of medicines regulation a necessity. Decreasing R&D costs, reducing drug lag, improving inter-agency cooperation and efficiency, and eliminating duplicative clinical trials are vital to ensure the health and continued growth of the pharmaceutical industry, which is saddled with one of the heaviest regulatory burdens of any industry. The ICH and international harmonization as a whole represent an exceptionally promising road to these goals.

In addition, society as a whole stands to gain from these propositions. International harmonization could lead to significant reductions in healthcare costs and drug prices. Such a development could improve healthcare not only in regions such as those represented in the ICH but also in the developing world. Moreover, international harmonization could certainly facilitate even greater strides in pharmaceutical science, and dreaded diseases could be swept away at an unprecedented pace.

However, although these grand visions are appealing, enthusiasm for international harmonization and its pioneer, the ICH, must be tempered with pragmatism. Europe's experience with drug regulation harmonization provides key insights that must be heeded if international harmonization is to succeed. A harmonized regulatory system like the one the ICH seeks to implement must present the industry with a choice superior to the current regime. In all likelihood, mutual recognition must be the foundation on which the harmonized system is based. In order to ensure the success of mutual recognition in the international arena, a sufficiently centralized scheme must be put into place with a strong central international authority.

Cause for pessimism certainly exists. Political and economic concerns will almost surely erect hurdles to the success of the ICH. Since these hurdles strike at the very principle of mutual recognition itself, the prospects of a strongly centralized international regulatory regime modeled after the EU system seem clouded. As the EU experience indicates, less robust schemes may

be doomed to failure.

Some hope can be seen, however, in the strong influence the industry wields in the development of drug regulation. This influence has been pronounced not only in Europe but in the United States as well, and developments in the near future may show the Japanese pharmaceutical industry starting to flex its muscle. Combined, these industry voices constitute an extremely powerful bloc, the importance of which is clear from its central role in the ICH. If recent history is indicative of the future, the eventual success of international harmonization is all but guaranteed. Still, successful international harmonization may not arrive in the form of the ICH since current concerns may prove too formidable at the present time.