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THE INTERNATIONAL CONFERENCE ON HARMONIZATION OF PHARMACEUTICAL REGULATIONS: PROGRESS OR STAGNATION?

David V. Eakin, M.D.

I. INTRODUCTION

Driven by its own destiny, the European Economic Community, now the European Union (hereinafter EU),¹ has sought to harmonize the regulatory laws of its member nations to "facilitate adoption of a common position by individual licensing authorities"² with respect to drugs. The project originally began in 1965. This led to establishment of a timetable for development of these guidelines originally expected to result in enhanced trade throughout the Community by 1985.³ That goal was not met nor has complete unification occurred in early 1999 at the time of this writing.

Seen as a desirable possibility for all major markets, exportation of the concept was attempted from 1988 onward. This was done through unilateral contact with Japan in 1988, and sponsorship of a joint conference including regulatory counterparts from Japan and the United States in 1989. This resulted in development of the structure for what is now known as the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (hereinafter ICH).⁴ At approximately the same time, the governments of several European countries and the United States, responding to a variety of influences, including consumer demands for improved access to new drugs and stagnation in the pharmaceutical industry, began to push for

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

2. See Joseph G. Contrera, Comment, *The Food and Drug Administration and The International Conference on Harmonization: How Harmonious Will International Pharmaceutical Regulations Become?*, 8 ADMIN. L.J. AM. U. 927, 939 (1995) (citing Leigh Hancher, *The European Pharmaceutical Market: Problems of Partial Harmonization*, 15 EUR. L. REV. 9, 13 (1990)).

3. See *id.* at 928 n.3 (citing GEORGE A. BERMAN ET AL., *CASES AND MATERIALS ON EUROPEAN COMMUNITY LAW*, 16, 18, 22, 23 (1993) (noting that the Treaty of Maastricht changed the name of the European Economic Community to European Union)).

4. See *id.* at 940.

greater efficiency of the drug approval process. The goal was to accomplish regulation for safety and efficacy with less cost and more expeditious access to drugs.⁵ The confluence of these political pressures and some limited progress in the development of a centralized regulatory mechanism within the EU resulted in Europe's regional imperative becoming a global cause for the three major economic powers: Japan; the United States; and the European Union.

The long-term goal of the ICH is to coordinate approval of new drugs to a single common standard developed by negotiation among the nations involved. It is hoped that this uniformity will cause acceptance of approvals generated outside any given country and thereby expedite international trade in drug products, lower research and development costs for pharmaceutical companies and eventually lower cost to the consumer. Currently, the standards and requirements for inspection vary widely. The U.S. through its regulatory agency, the Federal Drug Administration, (hereinafter FDA) has developed the most rigorous standards for drug approval. At times it has appeared less than enthusiastic about any modification of its programs by harmonization efforts. Several factors, including economic limitations within the agency, the substantial increase in world trade of drug precursors and products and growing political pressure to participate through linkage with mandatory trade agreements have caused greater cooperation by the FDA.⁶

The ICH process for development of Mutual Recognition Agreements (hereinafter MRA) in the area of drug control is now entering its final trial phase with the clear prospect that some sort of internationalized regulatory process will result. The lack of enforcement capability of the central agencies in the system may prove to be an invitation to continued intervention by member nations. This would prolong the approval process and add to the inspection burden of manufacturers. Currently, the yearly cost of FDA inspections alone is estimated at up to three billion dollars.

Considering the conflicting interests of the participants, the outcome is questionable. The vision of an optimized, universal, regulatory regime focused on consumer protection and ease of introduction of new drugs into the world market could be lost to regional distrust and continuing political barriers to the new system.⁷ This is the topic of this paper.

5. Kidd, *supra* note 1, at 184 n.1 (citing *Innovative Market Management Means Shooting Sacred Cows*, 9/26/94 MARKETLETTER available in 1994 WL 2717311; *See also 1993 in Europe - A New Internationalism*, 1/10/94 MARKETLETTER available in 1994 WL 2622184 (noting that pressures on the drug industry were without precedent in Europe). *Id.*

6. *See generally* note 1. *See also* Contrera, *supra* note 2.

7. Special Counsel Ansis Helmanis notes the unusual situation created for the FDA by its participation in creation of Mutual Resolution Agreements (MRA) which effectively bind the FDA to a recognition of "equivalence" of regulatory controls and standards of other countries. These agreements are being developed in a trade negotiations forum rather than a

The slow development of effective centralization of drug approval within the European Union to present, some thirty years from its conceptual beginnings in 1965, offers a microcosm of difficulties that may be anticipated with the global effort. With the prospect of a true central clearing mechanism with authority to bind its members still unrealized in Europe, questions are raised as to the real prospects for success of the ICH.⁸ Section I reviews the historical development of the harmonization process within the European Union.

Section II will evaluate the history of the FDA's development and the FDA activities directed toward implementation of the ICH goals. These activities have been impeded by an ambivalent attitude within the FDA and Congress toward the reliability of such an agreement, as well as by substantial fiscal restraints.⁹ Reliance on data from other regulators in a harmonized arrangement is a tempting goal for the FDA limited by severe fiscal restraints. On the other hand, the American consumer seems generally unwilling to accept any level of risk.¹⁰ Congress, reflecting the demands of its constituency and the limitations on funding, has also been ambivalent in its position. Because of this, Congress has intermittently pushed the FDA to perform redundant testing to insure its standards have been met contrary to the goals of the ICH. This fact has not gone unnoticed in the European Union and accordingly has evoked a general distrust of U.S. motives.¹¹

Section III will explore the divergent interests of the EU, Japan and United States, the major players in the harmonization process. The potential barriers to the successful conclusion of the International Conference on Harmonization are explored in detail.

health regulatory arena in which the FDA is accustomed to acting. The process of negotiating a binding trade agreement, subject to bargaining and trade-offs, is distinctly contrary to the FDA's usual single minded, authoritarian approach to dealing with quality and efficacy control issues. See generally *The U.S. - EU Mutual Recognition Agreement*, 1998 WL 11948481 [hereinafter 6/1/98 GOLDSHEET].

8. See Kidd, *supra* note 1, at 184.

9. 6/1/98 GOLDSHEET (discussing conflicting governmental demands and the limited ability of the FDA to respond due to a significantly increasing load of imports and inadequate fiscal resources).

10. Kidd, *supra* note 1, at 203.

11. See *US / EU Manufacturing MRA Requires "Confidence Building" - Sauer*, 11/30/98 PINKSHEET available in 1998 WL 8442447 (discussing the general cynicism of the FDA and Congress toward the outcome of the procedure) [hereinafter 11/30/98 PINKSHEET].

II. CENTRALIZATION OF DRUG APPROVAL WITHIN THE EUROPEAN UNION: A HISTORICAL PERSPECTIVE

The process of centralization of regulatory approval for drugs was begun in Europe in 1965 by the publication of Directive 65/65 EEC.¹² Action on the directive was not realized until 1975 when the Committee for Proprietary Medicinal Products (hereinafter CPMP) with its multistate procedure was implemented.¹³ Essentially, the CPMP was to function as a central clearinghouse for drug approvals submitted to any single European State by any one of the twelve member states of the European Economic Union.¹⁴ Once approval was sought in any single state, application could be made to as many as five states within the Union. Those States were required to consider the approval in the initial state when conducting their own reviews.¹⁵ Each state, by retaining broad authority to raise objections, could decide to reject a drug even though approved by the initial state of submission. This caused substantial uncertainty and effectively added another layer of approval without any apparent benefit in expediting market access. Essentially all submissions under this system resulted in objections that precluded their general approval.¹⁶

Because of the difficulties in the approval process, a new multi-state procedure, occasionally referred to as "mutual recognition," was implemented by the CPMP in 1975.¹⁷ The new system permitted drug companies to seek approval in a single state by making application to that state and the CPMP simultaneously. Once approval was obtained, the company could then apply to additional member states with the appraisal being forwarded to them.¹⁸ The member states had only ninety days to respond negatively, with approval being granted unless "there were grounds for supposing that the medicinal product concerned posed a public health

12. See Kidd, *supra* note 1, at 188 n.39 (citing Council Directive 65/65 EEC of January 26, 1965 on the *Approximation of Provisions Laid Down by Law, Regulation or Administrative Action Relating to Proprietary Medicinal Products*, 1965 O.J. (22) 269).

13. See Louis H. Orzak et. al., *Pharmaceutical Regulation in the European Community: Barriers to Single Market Integration*, 17 J. HEALTH POL. POL'Y & L. 847, 855 (1992).

14. Member States were not bound by the system and could still apply through the normal single country procedure for approval in any given state. See Kidd *supra* note 1, at 189.

15. See *id.* at 190.

16. See *id.* at 190 n.50 (citing a quote from a speech of C.A. Teijgler in *The Role of the CPMP in the EEC, in International Medicines Regulations: a Forward Look to 1992* (S.R. Walker and J.P. Griffin, eds. (1989)).

17. See *id.* at 190 n.53 (citing Council Directive 93/39 EEC of 14 June 1993 Amending Directives 65/65 EEC, 75/318 EEC and 75/319 in Respect of Medicinal Products, 1993 O. J. (L 214) 22; Richard F. Kingham, *Esq.* et al., *The New European Medicines Agency*, 49 DRUG & FOOD L. J. 301, 309 (1994)).

18. See Orzak, *supra* note 13, at 857.

risk.”¹⁹ Mutual distrust, similar to what occurred with the initial system, occurred under this regime. In the words of the CPMP Chairman, “[f]inal approval has clearly remained with the national bodies.”²⁰ By 1988, it had been noted by the CPMP that “there have been objections with regard to every case dealt with under the Multi-State [sic] procedure.”²¹ The committee further concluded that, “on the whole, the Member States do not yet accept each other’s assessment.”²²

The initial thrust toward true centralization of drug evaluation occurred in 1993, at which time the European Agency for Evaluation of Medicinal Products (EMEA) came into being.²³ The purpose of this agency is to coordinate the approval, manufacturing and inspection of medicines between the CPMP and member state’s regulatory bodies.²⁴ It functions only as an advisory body.²⁵ Since 1995, requests received by the EMEA have been forwarded to the CPMP for issuance of an opinion to the European Commission within 210 days. The Commission consults with its standing committee, the Standing Committee on Medicinal Products for Human Use.²⁶ An affirmative vote renders the acceptance final. If the Standing Committee rejects the proposal, the European Council must act within ninety days or the tendered rejection is automatically overridden, with the CPMP draft decision becoming final.²⁷ The net effect is to preclude rejection by member states individually as was possible under the CPMP mechanism prior to 1995.²⁸ This is not a binding regulation however. Each state’s national legislatures cannot be forced to accept the decision of the European Commission.²⁹ Thus far, this procedure has been used only for biotechnology products but is expected to be the *de facto* mechanism for other high-tech products.³⁰

The thirty-year vision of the European Union conceived in 1965, re-

19. See Kidd, *supra* note 1.

20. See Orzak, *supra* note 13, at 858.

21. See Kidd, *supra* note 1, at 190.

22. See *id.*

23. See *id.* at 190 n.53.

24. See *id.* at 192 n.80 (citing Evelyn Friedel & Michael Freundlich, *European Community Harmonization of the Licensing and Manufacture of Medicinal Products*, 49 FOOD & DRUGS L. J. 141, 160 (1994)).

25. See *id.* at 193.

26. The Commission has a standing committee, the Standing Committee on Medicinal Products for Human Use, which determines the fate of a proposal submitted by its vote. The committee is composed of members from all states but votes with a weighted majority. See *id.* at 193.

27. See *id.* at 193.

28. See *id.* at 193-194.

29. See Orzak, *supra* note 13, at 859.

30. See Kidd, *supra* note 1, at 193.

formulated in 1975, and currently overlaid by the EMEA remains unfulfilled. The inability to bind the member nations continues to be a serious hindrance. The success of this endeavor, as measured by reduced inspections or a decrease in time to market, remains subject to the pleasure of each member state's legislatures.³¹ The conflicting nationalistic attitudes delaying formation of the agency, may yet prove a substantial barrier to its final success.³² Viewed in this light, integration into a single, multinational, central control mechanism as proposed by the ICH seems destined to continue to meet with difficulty if not impossibility as discussed in section IV.

III. THE FDA, ITS CONGRESSIONAL MANDATE AND EFFORTS TOWARD INTERNATIONAL HARMONIZATION

The regulation of food and drugs in the United States of America began due to problems with drug safety and efficacy.³³ The Pure Food and Drug Act (hereinafter FDA) enacted in 1906, attempted to respond to those problems but contained many major flaws.³⁴ In consequence, numerous amendments were enacted over the next thirty years culminating in the passage of the extensively revised Federal Food, Drug and Cosmetic Act in 1938.³⁵ A public health disaster with Elixir Sulfanilamide in 1937 prompted enactment of this reform of the food and drug regulations.³⁶ The passage of legislation which had been under consideration for some time occurred almost immediately after the disaster. The resulting federal Food, Drug and Cosmetic Act of 1938 was the first legislation to address the safety of drugs. Imported drugs were also included

31. *Id.* at 191, n.61 (citing *No Rubber Stamp From Mutual Recognition*, OTC BUSINESS NEWS, Feb. 28, 1995, available in 1995 WL8375880 [hereinafter 2/28/95 OTC BUSINESS NEWS]).

32. 2/28/95 OTC BUSINESS NEWS (noting that in 1994, the EMEA director and the Commission pronounced that the member state's national authorities remain the "pillars" of the system).

33. Contrera, *supra* note 2, at 933 n.19. The history of federal imported drug regulation began in the 1800s with an Act regulating Smallpox vaccine. Subsequent to 19 deaths caused by a Diphtheria antitoxin contaminated with Tetanus bacteria, Congress enacted the Biologics Law of 1902 requiring licensing of establishments selling in interstate commerce. *See id.*

34. *See id.* at 934, n.22. (citing H.W. SCHULTZ, FOOD LAW HANDBOOK, (1981)).

35. The Sherley Amendment of 1912 was said to be the most important amendment concerning foreign importation. It included misleading or fraudulent claims of efficacy and benefits of a drug under the category of misbranded or mislabeled. *See id.*

36. A pediatric preparation of the "new" antibiotic Sulfanilamide was combined with ethylene glycol, antifreeze, as a solvent and carrier for dosing children. The toxic nature of antifreeze, previously not known, became clearly evident with the death of eighty seven children within a few months. *See id.* at 933, n.26.

in this legislation for the first time.³⁷ Subsequent to enactment, approval on the same basis was required before a drug produced outside the U.S. could be marketed in the United States.³⁸

The Thalidomide tragedy in England during the early 1960's prompted a second, significant overhaul of drug laws under the Kefauver – Harris Amendments. One of the most important changes was to require that the efficacy of a drug be demonstrated. This can only be determined by observation of the drugs effects on target conditions in humans. Accordingly, requirements for well controlled pre-clinical and clinical trials were established.³⁹

Recent initiatives in the area of pharmaceutical regulation have been directed at attacking what appears to be “drug lag” in the approval process in the United States.⁴⁰ The President's Council on Competitiveness, created in 1991, suggested, *inter alia*, increased reliance on and use of foreign data.⁴¹ Though this would suggest that harmonization would be an optimal means of achieving the mandated goal, the FDA viewed the idea with some suspicion. Accordingly, the FDA continued to require substantiation of efficacy and safety by domestic investigators. This was accomplished by incorporating a requirement that any proposed drug be submitted to at least one domestic clinical trial by an investigator considered competent by the FDA.⁴² The FDA justified this position by noting that:

1. foreign research protocols traditionally are less detailed than American protocols in terms of judgment and measurement of efficacy;
2. foreign researchers are unaccustomed to being closely monitored through recorded data;
3. acclaimed foreign researchers are less amenable to guidance from their sponsors;
4. human interpretation of statistical norms and computer programs differ across cultures;
5. foreign companies do not believe FDA standards are truly necessary; and
6. trial report documents in other countries contain less data than in the United

37. *See id.* at 935.

38. *See id.* at 934-935.

39. *See id.* at 935; *see also* n.35 (citing 21 C.F.R. § 312.23 (1963) describing provisions for an expanded process for Investigative New Drug applications).

40. *See* Michelle D. Miller, *The Informed-Consent Policy of the International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use: Knowledge is the Best Medicine*, 30 CORNELL INT'L L.J. 203, 234 (1997). (Noting that “drug lag” refers to the amount of time required for the approval process from conception to actual clinical use).

41. *See id.* at 235.

42. *See id.*

States.⁴³

As will be noted *infra*, many feel this stance is being pursued to the present time.

During this same time frame, the FDA benefited from passage of the Prescription Drug User Fee Act of 1992. The increased revenues generated permitted a substantial increase in enforcement personnel.⁴⁴ Coupled with the rigorous enforcement policies espoused by the FDA and expansion of regulatory efforts into the offshore bulk, raw material industry, the reach of the FDA has become increasingly global in direct conflict with the goals of harmonization.⁴⁵ (See discussion *infra* under MOU's.) The expansion of FDA regulation into this area of basic component production only enhances its global grip on standards, which in turn stifles the multilateral efforts of the ICH.⁴⁶

Currently, the FDA is pursuing two paths to maintain oversight on the drugs utilized by the American populace. Negotiations continue for implementation of "harmonization" but the major effort has been to develop "Memoranda of Understanding" (hereinafter MOUs) with foreign countries individually. These permit the FDA to dictate the terms of inspections and levels of quality in direct conflict with the announced goals of harmonization. Perhaps more importantly, this gives access to foreign sites not easily obtained under MRA's.

The FDA is strongly promoting and insisting on implementation of its Good Manufacturing Practices (hereinafter GMP)⁴⁷ for any agreement reached by the ICH mirroring its efforts with MOUs.⁴⁸ The FDA also questions some of the clinical practices of foreign practices as noted *supra*, and in consequence is promoting its "Good Clinical Practices" [hereinafter GCP] guidelines. The Good Clinical Practices directive is a proposal for an international ethical and scientific quality standard to be used exclusively for "designing, conducting, recording, and reporting trials that involve the participation of human subjects."⁴⁹

By its own admission, the FDA is pursuing harmonization as a secondary effort while maintaining its primary mission of domestic drug control. This is due primarily to fiscal restraints.⁵⁰ Recently, somewhat

43. *Id.* at 235.

44. *See* Kidd, *supra* note 1, at 196.

45. *See id.* at 199.

46. *See id.*

47. *See id.* at 200.

48. International Conference on Harmonization; Good Clinical Practice: Consolidated Guideline; Notice of Availability, 62 Fed. Reg. 90, 25,692 (1997) [hereinafter 62 Fed. Reg. 90].

49. *Id.*

50. *See* Kidd, *supra* note 1, at 202 (quoting David Kessler, head of the FDA).

brighter prognostications are emerging though at least one observer has commented that it "appeared to the EU at times that what 'MRA' meant to the U.S. was 'my regulations apply.'"⁵¹

The U.S. House Commerce Committee, the oversight committee for the FDA, has recently raised questions as to the overall effectiveness of MRAs in light of what they consider to be more stringent FDA requirements for safety.⁵² House testimony by the deputy commissioner of the FDA, Sharon Smith Holston, indicated, however, that no compromise of FDA standards was implied by the US entering into the third phase of implementation of harmonization. She noted that the agency had initially raised the issue of shared inspections with its European counterparts.⁵³

Lacking the capacity and funding to inspect foreign companies at the rate required to maintain safety, she commented that the overall result would be beneficial in the long run. Commencing in December of 1988, the final, three year, trial implementation of the Mutual Recognition Agreement is being evaluated.⁵⁴ Holston noted that of the fifteen EU member states, decisions by the FDA as to acceptability would involve only two or three of the states with the highest exportation levels.⁵⁵ This is certainly less than a universal appraisal and may provide a basis for further requests by the FDA for delays. An even less optimistic opinion was suggested by Ferdinand Sauer, executive director of the European Medicines Evaluation Agency. During a conference in London in November 1998, he stated "FDA officials are cynical about the outcome of the process ..." in referring to the primary responsibility of the U.S. participants to develop GMP's.⁵⁶

As noted, implementation of the three year trial is scheduled to begin in December, 1998. The fear of compromise of safety and efficacy standards still pervades the U.S. position.⁵⁷ Some have commented that the U.S., by participating, is selling-out to the national desire for trade, rather than reflecting appropriate concern for consumer safety.⁵⁸

IV. CONFLICTING INTERESTS AND PROSPECTS FOR THE SUCCESS OF MUTUAL RECOGNITION AGREEMENTS

51. 6/1/98 GOLDSHEET, *supra* note 7.

52. See *U.S. House Panel's Fears over EU MRA Inspections*, 10/12/98 MARKETLETTER available in 1998 WL 17365974 [hereinafter 10/12/98 MARKETLETTER].

53. See *id.* (Seemingly, this contradicts previous position statements. See *supra* note 42.)

54. See 1/30/98 PINKSHEET, *supra* note 11.

55. See *id.*

56. *Id.* (quoting Dan Barton (R-Texas) as stating "the pharmaceutical annex was included at the insistence of the Europeans and appears to open few doors for increased American pharmaceuticals in Europe." *Id.*)

57. See 10/12/98 MARKETLETTER *supra* note 52.

58. See *id.*

The European harmonization system has continually suffered from the lack of a central enforcement authority empowered to impose its actions upon member countries. The same appears to be the Achilles' Heel of the ICH in developing the MRA. The individual country's legislatures continue to have final control of implementation with the attendant political uncertainties.⁵⁹ Without enforcement procedures built into the central system to assure compliance, member countries retain a potential "veto" which in turn jeopardizes the entire system.

This is particularly applicable to the U.S. where ambivalence, both by the legislature and the FDA, seems to be the rule. The U.S., not content to rely on what it may feel are unsubstantiated and uncontrolled foreign clinical and manufacturing practices, may well continue to develop MOUs.⁶⁰ As noted, MOUs permit the FDA to impose its more stringent standards on foreign countries and also serve to provide authorization for foreign inspections.⁶¹ Effectively, this adds another layer of inspection which potentially slows the overall process through unnecessary redundancy. The result negates the purpose of harmonization.⁶² Other barriers to implementation of the Mutual Recognition Agreement for pharmaceuticals are discussed below.

A. *Ethnic and Cultural Barriers*

Ethnic and cultural differences are reflected in differing attitudes toward health, medicine and doctors generally. They pose a major obstacle to successful development of pharmaceutical standards, particularly in the conduct of clinical trials.⁶³ Miller, in an extensive presentation of differing approaches to informed consent, comments that the "paternalism" of Japanese investigators and the tendency in the EU to favor medical progress over fully informed consent raise "troubling issues."⁶⁴

There have been eleven major drug disasters in Japan over the last forty years resulting in the deaths of several hundred people and exposure to risk of up to 20,000 people.⁶⁵ Multiple factors appear to be involved including:

1. a 'paternalistic' attitude of Japanese physicians toward informed consent with many patients not being told that they have been placed on an experimen-

59. Conterera, *supra* note 2, at 954-955.

60. See Kidd, *supra* note 1, at 200.

61. See *id.* at 202.

62. 6/1/98 GOLDSHEET *supra* note 51 (discussing generally the pressures facing the FDA).

63. See Kidd, *supra* note 1, at 203.

64. Miller, *supra* note 40, at 234, 227.

65. See *id.* at 222. Japanese physicians have substantial discretion in choosing to treat hospitalized patients with experimental drugs without their knowledge or consent.

tal drug;

2. the ability of drug companies to suppress unfavorable data without significant penalty; and
3. the overriding profit motive.⁶⁶

Yet another factor impacting upon the drug disasters in Japan is the \$2,600 reimbursement paid to the hospitals for each case.⁶⁷ Kickbacks to meagerly reimbursed doctors are also the rule. One estimate suggests that upwards of 20 billion dollars per year is dispensed in this manner.⁶⁸ This is rather interesting considering that Japan appears to be slated to oversee the efficacy standards for drug testing.⁶⁹ This undoubtedly explains the U.S. insistence on acceptance of the Good Clinical Practice standards which include incorporation of the Helsinki agreement on informed consent.⁷⁰

Informed consent became an issue in Japan after the Sorivudine crisis in the 1980's. Sorivudine, an anti-viral drug that had previously been rejected in Europe as too dangerous but was marketed in Japan by Nippon Shoji, hoped to increase the value of its shares in a forthcoming stock issue.⁷¹ The drug resulted in eight deaths within three weeks, as well as severe, chronic effects in those who survived.⁷²

Consumer groups demanded reform of the consent practices. The resulting guidelines only suggested written documentation and did not modify the physician's discretionary ability to place patients on experimental drugs without full informed consent.⁷³ A more recent incident with Irinotecan, an anti-cancer agent, has caused renewed efforts to improve the informed consent of patients in trials and to require written confirmation of receipt of informed consent.⁷⁴

Even with the renewed initiative, only approximately fifty percent of Japanese doctors believe that it is necessary to obtain written consent.⁷⁵ Perhaps more importantly, doctors still describe informed consent as a "doctor's explanation" and a "patient's consent."⁷⁶ This stands at the op-

66. *See id.* at 222-224.

67. *Id.* at 222 n.150 (quoting a Sydney Morning Herald article from July 1994).

68. *See id.* at 240.

69. *See* Jill Weschler, PHARMACEUTICAL EXECUTIVE, (6/1/1998) available in 1998 WL 13270667 [hereinafter PHARMEEXEC].

70. *See* 62 FED. REG. 90 *supra* note 48, at 25692.

71. *See* Miller, *supra* note 40, at 223.

72. *See id.*

73. *See id.* at 225.

74. *See id.* at 226 n.196 (quoting an official of the Japanese Pharmaceutical Affairs Bureau as reported in COMLINE DAILY NEWS BIOTECH AND MED. TECH. (11/14/1994)).

75. *See id.* at n. 200 (quoting a poll done by COMLINE (09/12/1995)).

76. *See id.* at 226 n.201 (quoting an article from the Daily Yomiuri 12/5/1992 reflecting

posite end of the spectrum from the U.S. that emphasizes self-determination as the paramount consideration for adequate informed consent.⁷⁷ Accordingly, if the ICH standard of the informed consent reflects this diminished standard, there will be a direct conflict with established case law in the U.S. protecting patient rights.⁷⁸

Other ethnic factors affecting acceptability of foreign data involve those which are culturally driven such as: diet; smoking habits; use of alcohol; exposure to pollution; amount of daily sunshine; socioeconomic status; and compliance with prescribed drug regimens.⁷⁹ These elements are particularly crucial to determinations of drug equivalence, as well as efficacy.⁸⁰ Intrinsic ethnic factors impacting on equivalence include: genetic polymorphism; average age; gender; height; weight; lean body mass; body composition; and organ dysfunction.⁸¹ An additional factor that has been of great importance in Japan has been the co-use of other drugs.⁸² According to Miller, the Japanese take twice as much medications as Americans, as evidenced by approximately \$80 billion that are expended yearly. This has resulted in a derisive phrase for the Japanese, "kusuri zuke shaki," which translates to "drug-pickled society."⁸³ The potential for uncertainty and conflicting results from this fact alone is of considerable concern.

B. Political Barriers

Political barriers also pose a potential problem. Legislatures retain the final ability to approve or reject standards, as well as the capacity to change requirements at any time. This is potentially disruptive⁸⁴ of the entire system.⁸⁵ Several authors have noted the close relationship of drug regulatory activities and public policy in any given country.⁸⁶ Ceding this control to a central agency would prove essentially unworkable for many states which view regulation of drugs as synonymous with national sov-

the statement by Masao Onishi that doctors "arrogantly dispense what ever treatment he deems best").

77. *See id.* at 227.

78. *See id.*

79. *See generally*, International Conference on Harmonization; Guidance on Ethnic Factors in Acceptability of Foreign Clinical Data 63 FED. REG. 31,790 (1998).

80. *See id.* at 31,794 (defining equivalence as the extrapolated response to drugs from the standpoint of safety, efficacy, and dose-response).

81. *See id.*

82. *See* Miller, *supra* note 40, at 239-240.

83. *Id.*

84. *See* Orzak, *supra* note 13, at 865.

85. Contrera, *supra* note 2, at 954-955.

86. *See generally* Orzak, *supra* note 13 (noting the conflicts between a single nationalized or internationalized system and a regulatory body controlled locally).

ereignty.⁸⁷ Given the strong relationship of culture and society to ideas concerning public health, drug control remains essentially a political entity.⁸⁸ A prime example may be the FDA which remains essentially a creature of Congress, subject to the political whims and shifting positions of special interest groups.⁸⁹

In large part, this conflict has led to the structuring of the ICH without any central enforcement capabilities.⁹⁰ The FDA seemingly views this defect as an invitation for it to attempt to fulfill an oversight function within the international community through continued development of MOU's with individual countries. As noted, this permits foreign access that is otherwise not available under the MRA without first seeking permission.⁹¹ This approach is entirely contrary to the express goals of the ICH.

The approach of the FDA conflicts with the directive of the General Accounting Office (hereinafter GAO) which has proposed cooperative acceptance of "foreign" inspection and approval data.⁹² The FDA's goal should be "to 're-examine and revise' its foreign inspection strategy to provide adequate assurance that all foreign manufacturers exporting approved pharmaceutical products to the U.S. comply with U.S. standards."⁹³ At a minimum, the major strategic initiatives should include, "(1). timely follow-up inspections of all foreign manufacturers that have been identified as having serious manufacturing deficiencies and that have promised to take corrective action; and (2). periodic surveillance inspections of all foreign manufacturers, not just high risk manufacturers."⁹⁴

The key concern of the GAO was timeliness. According to the GAO, sixty percent of the reports submitted by foreign inspection agencies were later than those called for by agency standards. That included fifty percent regarding companies with the most serious deficiencies. In addition the FDA response time to this notice was almost four times as long as normally provided.⁹⁵ The clear implication of these observations was that the FDA may be compromising its own standards to accommodate harmonization.

The industry has expressed fear that, with the uncertainties of a har-

87. See Kidd, *supra* note 1, at 203.

88. See *id.*

89. See 6/1/98 GOLDSHEET, *supra* note 7; 11/30/98 PINKSHEET, *supra* note 11; Oct. 12, 1998 MARKETLETTER, *supra* note 52.

90. See Kidd, *supra* note 1, at 194-195.

91. See *id.* at 200.

92. See 6/1/98 GOLDSHEET, *supra* note 7.

93. *Id.*

94. *Id.* (citing the final GAO report of April 1998).

95. See *id.*

monized, regularized system, more rather than less inspection burden may result.⁹⁶ A Glaxo Wellcome executive framed the transition period in the following terms: "[t]he transition period itself gives a lot of worry to industry, because we see it being a time when there can be a substantial escalation of standards for no real benefit. There can be periods of over regulation, there can be increased regulator activity."⁹⁷ This Glaxo Wellcome executive further stated that "over-regulation" may potentially lead to "technology block."⁹⁸

C. Criminal Activities

Criminal activities have become an increasing problem with third world countries entering the drug supply chain. This activity is evidenced by a recent incident in Haiti in which eighty-nine children were poisoned by glycerin containing ethylene glycol,⁹⁹ an event strikingly similar to the Sulfanilamide disaster in the U.S. leading to the Harris-Kefauver Amendments.¹⁰⁰ Eli Lilly & Company have identified five types of criminal activity which should be guarded against:

1. Unproved generics;
2. Product diversion;
3. Counterfeit Labels;
4. Counterfeit API's (active ingredients); and
5. Counterfeit drug products.¹⁰¹

Frequently, counterfeit drugs are placed into the system by India and China and are made to resemble the "copied" drug. Most commonly, counterfeits appear during the legal transition of protected drugs to generics. The sellers often escape detection by claiming that a marketing application is pending with the FDA. The lack of investigation and prosecution in some countries makes it impossible to stop such activity. Additionally, the FDA and U.S. government do not have an integrated plan for enforcing prohibitions against such activity, which has resulted in many counterfeit drugs escaping detection until they reach the consumer

96. *See id.*

97. *Id.*

98. *Id.*

99. Sulfanilamide was one of the first antibiotics manufactured in the U.S. S.E. Massengill, looking to bring the product onto the market for children, utilized ethylene glycol (*i.e.*, antifreeze, not known to be toxic at that time) as a solvent to create a syrup. Eighty-seven children died from the use of this drug. *See id.* at 934, n.26.

100. The Kefauver-Harris Amendments required that a new drug had to be safe and "effective." They also promulgated new standards for clinical trials with emphasis on efficacy and safety. *See Contrera, supra* note 2, at 934 n.35.

101. 6/1/98 GOLDSHEET, *supra* note 7.

level.¹⁰²

A similar situation exists with what is known as "parallel importation" or "U-boat" sales.¹⁰³ "Parallel importation" or "U-boat" sales occurs with diversion of products obtained by countries which are able to negotiate the most favorable rates from the manufacturer. Here, the result is to defraud the manufacturers by re-importing their own products, which are then sold on the open market at a substantial discount and profit to the "importers". The EU countries currently have no policies precluding this activity which contributes to the problem.¹⁰⁴

Counterfeit active pharmaceutical ingredients (API) obtained in bulk from foreign importers also pose a substantial threat to the manufacturers of generic drugs. This problem is occurring frequently due to the substantial profits that can be realized from such transactions. The magnitude of counterfeiting has increased notably in recent years with as much as forty to sixty percent of the drugs sold in Malaysia being counterfeit, twenty-five percent in Mexico and perhaps seven percent in the U.S.¹⁰⁵

D. Trade Agreements Versus Regulatory Controls

Another troublesome feature of the overall process is that it is inextricably tied to trade negotiations.¹⁰⁶ This seriously limits the FDA's ability to impose what many feel and acknowledge are higher standards than those being proposed for the Mutual Recognition Agreements.¹⁰⁷ Some observers have noted that the disparity in national goals may cause some to push for "downward" harmonization to promote freer trade rather than "upward" harmonization which would guarantee greater levels of protection to consumers worldwide.¹⁰⁸ In the U.S. there exists essentially no tolerance for diminished protection, contrary to third world countries which are accustomed to limited, or no protection by their governments. Any perceived diminution in standards could pose serious political and legal conflicts.¹⁰⁹ The latter derives from the fact that no recourse to the legal system is created for injuries sustained during, or as a result of, flawed preliminary studies.¹¹⁰ In part, this is due to the rather severe limitations placed on establishment of standing¹¹¹ to sue by cases such as

102. *See id.*

103. *Id.*

104. *See id.*

105. *See id.* (citing director William Grosse of Eli Lilly & Co.).

106. *See id.* 10/12/98 MARKETLETTER, *supra*, note 52.

107. *See id.*

108. Kidd, *supra* note 1, at 195.

109. *See* 6/1/98 GOLDSHEET *supra* note 7.

110. Miller, *supra* note 40, at 234-237.

111. *See id.* at 237-238 (established that standing for beneficiaries of an agency action is directly dependent on a showing of that beneficiary's direct relationship to the challenged

Lujan v. Defenders of Wildlife.¹¹²

The participation of the FDA in the trade negotiations, which form an umbrella over the ICH endeavor, is only a limited part of more involved discussions and agreements. Generally, the negotiations are part of the General Agreement on Tariffs and Trade (GATT) and also under a section of Technical Barriers to Trade (TBT). Additionally, the FDA has participated in the World Trade Organization (WTO) and North American Free Trade Agreement (NAFTA) negotiations in an attempt to further facilitate international trade.¹¹³ The resulting effect has been to subordinate normal regulatory goals to the creation of more freely accessible trade exchanges.¹¹⁴ Under the most recent TBT agreements, each country may maintain control of its definitional standards, but once it has agreed to common international standards, it is bound to the latter with severely restricted latitude to act on its own.¹¹⁵ Similar procedures and arrangements are standard for NAFTA and WTO agreements as well.¹¹⁶

Accordingly, the FDA and U.S. Congress, normally accustomed to much greater control, are potentially subjugated to the will of the international community. This situation has led some congressional members of the House Oversight Committee to comment that "trade pressures may be trying to outpace health and safety issues in the agreement."¹¹⁷ In turn, this emboldens the FDA to demand further access for its own inspections, which partially defeats the entire intent of the agreements (reduction of the overall number of inspections by recognition of foreign regulatory control mechanisms). This contradiction is noted by Weschler who quoted the deputy director of Center for Drug Evaluation and Research, Roger Williams, as stating that, "FDA reviewers need 'strong' justification and supervisory concurrence to deviate from ICH standards. The guidelines should provide a 'ceiling' for what data reviewers may request, and not a 'floor' subject to additional requirements in each region."¹¹⁸

Kidd comments that recent congressional approval of increased enforcement initiatives and the extension of the Drug User Fee Act for five years conflicts directly with ICH initiatives and may suggest future

action).

¹¹². Lujan v. Defenders of Wildlife, 504 U.S. 55 (1992). (established that standing for beneficiaries of an agency action is directly dependent on a showing of that beneficiary's direct relationship to the challenged action).

¹¹³. See International Harmonization; Policy on Standards: Notice, 60 FED. REG. 53077, 53079 (1995) [hereinafter 60 FED. REG.].

¹¹⁴. 10/12/1998, MARKETLETTER, *supra* note 52.

¹¹⁵. See 60 FED. REG., *supra* note 48, at 53079.

¹¹⁶. See *id.*

¹¹⁷. 10/12/1998 MARKETLETTER, *supra* note 52.

¹¹⁸. Wechsler, *supra* note 70.

problems with the incorporation of ICH standards.¹¹⁹ The increased funding from the Drug User Fee Act also helps to diminish the effect of fiscal restraints which, according to Holston, is the major factor pushing the FDA toward compliance.¹²⁰ The binding character of these trade agreements and the potential exclusion of the U.S. from a forty billion dollar market would seem to be a strong disincentive tending to contradict Kidd's hypothesis.¹²¹

Foreign observers have noted these ambivalent and sometimes contradictory positions of Congress and the FDA. Commenting on a speech by FDA International Policy Director Linda Horton, Special Council Ansis Helmanis made the following observations:

1. the FDA historically has been accustomed to entering into non-binding MOUs as opposed to the binding character of trade pacts;
2. the MOUs were voluntarily negotiated between health authorities rather than being subject to the politics of trade agreements where trade-offs are the rule, rather than the rare exception; and
3. MRAs are binding trade pacts and thus withdrawal is not an option for the FDA.¹²²

Congress, which ultimately dictates much of the FDA policy, is wary of the potential negative effects of ceding a large measure of control to a foreign entity. It has demonstrated this concern by its ambivalence toward the ICH.¹²³

E. Patent Laws

According to Kidd, there is "strong evidence that the vitality of any modern health care system is directly dependent upon a strong intellectual property regime."¹²⁴ Currently, patent laws vary substantially worldwide with little apparent potential for a harmonized intellectual property

119. See Kidd, *supra* note 1, at 197.

120. See 10/12/98 MARKETLETTER, *supra* note 52.

121. See 6/1/98 GOLDSHEET, *supra* note 7.

122. *Id.*

123. *Id.*

124. Kidd, *supra* note 1, at 205 n.176. An example of problems arising from limited protection are noted in India's recent failure to pass modifying legislation in this area. Although plagued by epidemics of easily treatable diseases, India is currently avoided by most drug manufacturers due to poor patent protection. See *Indian Industry Seminar Discusses Patents*, MARKETLETTER, May 22, 1995 available at 1995 WL 2152963 [hereinafter 5/22/1995 MARKETLETTER]; A similar situation existed in China even though it represented 22% of the world population; *U.S. Industry Welcomes China Trade Treaty*, MARKETLETTER, March 6, 1995 available at 1995 WL2151973. [hereinafter 3/6/1995 MARKETLETTER].

system.¹²⁵ Sabetelli and Rasser feel this is due to:

1. [t]he reluctance of national governments to give up their current systems which allow them to use their patent laws to favor domestic entrepreneurs;
2. [t]he relinquishment of a portion of national sovereignty for the sake of a global system; and
3. [t]he reconciliation of the different national interests of the developing countries (*i.e.*, the Third World) and the developed countries.¹²⁶

The authors further note that it is essentially these same three core issues which have and will prove to be significant impediments to international harmonization in many areas of endeavor.¹²⁷

A major stumbling block in the area of patents is the U.S.'s resistance to adoption of a "first to file" system for patent recognition.¹²⁸ The "first to file system" is the *de facto* international standard in contrast to the "first to invent" system used and supported by some 200 years of case law in the U.S.¹²⁹ Admittedly, a change would require statutory amendment of a firmly entrenched system. However, as pointed out by the authors, most U.S. companies doing business internationally are currently working under the "first to file" system without difficulty.¹³⁰ The U.S. position on this aspect of harmonization is strikingly similar to the FDA's insistence on negotiating individual MOUs, "my rules apply" as noted above

Other significant obstacles also exist which have been the subject of continuing negotiation during eight rounds of the GATT extending over forty-eight years. The recent resistance of India to implementation of stronger intellectual property laws is one example.¹³¹ The other areas of dispute are:

1. automatic publication of all patent applications 18 months after filing (not

125. See Anthony D Sabetelli & J.C. Rasser, *Impediments to Global Patent Law Harmonization*, 22 N. KY. L. REV. 579-580 (1995).

126. *Id.*

127. *Id.* at 581.

128. *Id.*

129. The authors note that the U.S. and Philippines are the only countries to adopt the "first to invent" system. (citing Lee J. Schroeder, *The Harmonization of Patent Laws*, C576 A.L.I. 473, 475 (1990). See *id.* at 587 n.27.

130. *Id.* at 606.

131. India's need for a strong intellectual property rights regime was discussed by Richard Arnold of the International Pharmaceutical Manufacturer's Association at a seminar on the topic in New Delhi in 1995. The Parliament's failure to pass such legislation caused India to be placed on a "priority watch list" by America's trade representative, Mickey Kantor. 5/22/95 MARKETLETTER, *supra* note 124.

- currently done in the U.S.);
2. granting prior user rights to those in possession of an invention at the time of filing by another;
 3. recognition of non-published foreign prior art as a statutory bar to patentability;
 4. adoption of the filing date as the effective date of a foreign patent application for prior art purposes;
 5. granting of interim patent protection; and
 6. adoption of a uniform term of patent protection.¹³²

Complicating all of these issues is the heavy involvement of third world nations in the negotiation process with demands for recognizing "special needs." The recent acquiescence of China to stronger enforcement of trademark and patent rights is viewed with skepticism due to its wish not to be excluded from the WTO.¹³³ Considerable hostility to GATT exists within the U.S. Because of this hostility, prompt resolution of these issues does not seem imminent.¹³⁴

F. Regulatory Creep

Kidd also notes that "mission creep" endangers the entire process.¹³⁵ Other subjects for harmonization have been inserted into the framework of the Mutual Recognition Agreements that tend to complicate the entire process.¹³⁶ Rather than concentrating on issues uniquely associated with control of production and quality of drugs, standards for such diverse things as watercraft, lawnmowers and electromagnetic radiation are also being developed under the general umbrella of the MRA.¹³⁷ Though consumer safety is a common thread, the means and methods of defining and insuring it vastly differ, thereby limiting the potential for optimal resolution of issues specific to drugs.¹³⁸

132. *Id.* at 605.

133. China, on the other hand, agreed to a U.S. China trade treaty which included stronger enforcement of patent and trademark rights. Many felt their agreement was only due to the prospect of exclusion from the World Trade Organization and consequently are taking a wait and see attitude. See 3/6/1995 MARKETLETTER, *supra* note 128.

134. *Id.*

135. Kidd, *supra* note 1, at 205 n.179 (defining mission creep as expansion of original objectives to include less focused and less realistic goals).

136. AGREEMENT ON MUTUAL RECOGNITION BETWEEN THE UNITED STATES OF AMERICA AND THE EUROPEAN COMMUNITY, www.iep.doc.gov/mra/mra.htm (including telecommunication equipment, electromagnetic compatibility, electrical safety, recreational craft and medical devices as Sectorial Annexes to the Mutual Recognition Agreement).

137. See 6/1/1998 GOLDSHEET, *supra* note 7.

138. See *id.*

G. *Problems with Fast Track Drug Approval in the U.S. and Canada*

Recently, the FDA has shown a more conciliatory attitude toward the ICH concept.¹³⁹ A similar concept was supported by the Bush White House in 1990. President Bush, continuing the original limited reforms initiated by President Carter, mandated that faster approvals of new drugs should be sought by several measures.¹⁴⁰ These suggested measures in relevant part were:

1. use of external review;
2. expanded use of advisory committees;
3. an expanded roll for Institutional Review Boards;
4. flexible interpretation of the efficacy standard;
5. accelerated approval;
6. Expanded use of foreign data and recognition of foreign approvals ...; and
7. direction of staff and financial resources toward new drug reviews.¹⁴¹

As previously noted, the FDA has intermittently resisted such a change in policy. This was particularly evident under the leadership of Kessler whose policies emphasized increased enforcement and expansion of FDA investigative activities.¹⁴² Inclusion of new areas such as bulk ingredient producers and foreign operations occurred during his regime by the use of MOUs.¹⁴³

Under continued pressure from consumer groups and politicians, the FDA has finally embarked upon the proposed new task domestically.¹⁴⁴ With the passage of the Food and Drug Administration Modernization and Accountability Act of 1997, the Clinton administration has nudged the FDA into expediting consumer access by placing some drugs on fast track approval. The key element has been the re-authorization of the User Fee Act which provides funding and allows for outside expert reviews.¹⁴⁵ Countering assertions of diminished safety, people inside the agency note that the FDA retains substantial discretion.¹⁴⁶

In an attempt to dispel the asserted need for the FDA's retention of control, Mark E. Grayson, assistant VP of the industry group at the Phar-

139. See Miller, *supra* note 40, at 228 (citing more rapid access and decreased cost to consumers as the two major goals of harmonization).

140. See *id.* at 234 n.261 (citing Recommendations to Speed Drug Approvals Issued [1990-91 Transfer Binder], FOOD DRUG COSM. L. REP. (CCH) p.42,603 at 43617).

141. *Id.*

142. See Kidd, *supra* note 1, at 199-202.

143. See *id.*

144. Thoroughly Modern, 1/1/1998 MEDANEWS 1, available in 1998 WL 10478901 [hereinafter 1/1/98 MEDANEWS].

145. See *id.*

146. See *id.*

maceutical Research and Manufacturers of America, has stated that "I don't think the approval process can get too fast," while simultaneously defending the 1997-1998 American Home Products disaster with the weight loss drug Redux.¹⁴⁷ Considering the significant number of deaths resulting from tricuspid valve (TV) damage, the resultant pulmonary hypertension, and more importantly, the large number of patients with now asymptomatic TV damage (whose outcome is currently unknown), this seems a rather self-serving remark by an industry driven mostly by profit motive.¹⁴⁸ Michael A. Friedman's prognostication that with faster market access, manufactures should show a profit gain of four percent domestically from 1997 to 1998, and eight percent for foreign based companies, also seems to support this conclusion.¹⁴⁹

The significance of the overriding profit motive is further substantiated by an article in the *Globe and Mail*, by authors Krista Foss and Paul Taylor, which illustrates "the uneasy tango between pharmaceutical companies and the academics they use to test their drugs."¹⁵⁰ Dr. Olivieri, a researcher at Toronto's Hospital for Sick Children, has been threatened with legal action by a pharmaceutical manufacturer for attempting to publish negative findings with regard to their drug. The authors note that "when the profit motive takes precedence over scientific rigor - or worse, patient's safety - that researchers are compromised."¹⁵¹ The authors, quoting Martin Schecter, National Director of the Canadian HIV Trials Network, further note that "[w]hen corporate interests are funding research, often they have an agenda for what that research will show and how it will help their corporate endeavors."¹⁵²

Citing costs for an upcoming trial of the heart drug Fradifiban, Foss and Taylor also emphasize that Canadian Universities and hospitals are to receive approximately \$5 million dollars. Physicians involved will be paid up to \$10,000 per patient - this amount sometimes exceeds \$20,000. Additionally, the testing firm will pay the hospital \$25,000 to "cover costs of light, heat, and electricity used by each patient while hospitalized." By playing "ball" with the manufacturers by not publishing negative results, researchers, hospitals and universities stand to reap a substantial, continuing benefit.¹⁵³

In a similar incident, Dr. Betty Dong, a researcher at the University

147. *See id.*

148. Personal opinion of the author.

149. *See* 1/1/1998 MEDADNEWS, *supra* note 144.

150. Krista Foss & Paul Taylor, *Volatile Mix Meant Trouble at Sick Kid's Hospital, Revolt Illustrates the Potential Danger of Marrying Profit and Scientific Research* 8/22/1998 *GLOBE & MAIL* (TORONTO CAN.) A1 [hereinafter 1/1/98 *GLOBE & MAIL*].

151. *Id.*

152. *Id.*

153. *Id.*

of California at San Francisco, sought to publish negative results on the relative efficacy of Synthroid versus a cheaper generic substitute. After seven years (four under threat of legal action that culminated in her being dropped by the university), and with the support of the FDA, she was able to publish the results in the *Journal of the American Medical Association*. In a similarly unfortunate situation, researcher David Kern, MD., founder of the occupational and environmental health services at Memorial Hospital of Pawtucket, R.I. and Brown University, lost both appointments one week after publishing a negative report as to incidence of lung disease in a local textile manufacturing plant, Microfibres, Inc. This terminated ten years of service to both entities.

Foss and Taylor acknowledge that these cases are only three among perhaps thousands where research is being carried on without problem.¹⁵⁴ They do cite other statistics that evoke the same sense of possible conflict.

1. In the U.S., medical research is funded annually in the overall amount of \$30 billion dollars. \$16 billion dollars comes from private industry sources. With public funding of universities and hospitals diminishing due to budget constraints, some observers predict a potential for increasing control of the dispersion of results by drug companies.
2. A Carnegie Mellon study has recently shown that thirty-five percent of research agreements allow the sponsor to delete information from the report, fifty-three percent permit delays in publication.
3. A recent survey of 2000 members of science facilities by Harvard Medical School showed that forty-three percent had received some sort of a gift from pharmaceutical companies in the last three years.
4. Researcher self interest is also a potential problem. Recently, a researcher publishing a favorable report failed to mention that he held a patent on the product.¹⁵⁵

With diminishing reimbursement for patient care, many hospitals may seek to increase their revenues by attracting more drug trials or restructuring to develop an operation supportive of and conducive to entering into this lucrative field.¹⁵⁶ One such example is the Children's Hospital in Columbus, Ohio. Though portrayed by the Children's Hospital as "good for pediatricians, good for kids, good for pharmaceutical companies and good for the FDA," the real "good" of the proposed project to increase access to clinical studies would appear to be on the bottom line.¹⁵⁷

154. *Id.*

155. *Id.*

156. *Id.*

157. *Children's Hospital Hopes to Win More Clinical Trials*, 9/16/98 COLUMBUS DISPATCH

When considered in the light of alternatives which have included hospital closings, physician bankruptcies, and interpolation of third party payers into the costs of hospital operation, it is of no wonder that hospitals are looking to more secure sources of income. Equally anticipated may be results as described above with researchers Oliveri, Kern and Dong. Such propensities make ceding of FDA control to a remote foreign entity with no personal stake in the outcome, nor possibility of legal accountability becomes a rather tenuous proposition.

The lack of direct accountability might lead to a situation as experienced in Japan with the Sourivudine crisis where two of the three deaths were kept secret because, as a former executive explained, "[i]t is normal (in the pharmaceutical industry) to close your eyes to bad data ... it would be a big problem if a drug which cost billions of yen to develop were not approved."¹⁵⁸

V. SUMMARY

International control of drug approval and evaluation appears to run counter to the long-standing political interest of individual countries.¹⁵⁹ As noted, health policy is inextricably tied to cultural and societal values in any given society and as such has always been subject to intense politicizing by regional and national governments.¹⁶⁰ In developing countries, the primary goal may be to provide drug access regardless of efficacy and safety. The production of drugs and active primary ingredients is extremely profitable if removed from the constraints of scrupulous and rigorous testing. This may provide additional impetus for limited scrutiny in cash poor countries.

The thrust of U.S. drug policy is diametrically opposed to such a philosophy. The American consumer has essentially no tolerance for risk with respect to drugs, and in consequence the FDA has developed and continues to pursue inordinately high standards.¹⁶¹ The EU countries tend to pursue a middle ground giving individual investigators substantial discretionary control of clinical trials.¹⁶² These divergent ideas regarding informed consent, medical practice, and health issues also pose serious

(OHIO) 05C available in 1998 WL 16493856 (noting the hospitals scramble to be included in newly funded pediatric drug trials).

158. Miller, *supra* note 40, at 223 n.156 (quoting a former Nippon Shoji executive as reported by Ben Hills, *Japan: Prescription for Disaster*, SYDNEY MORNING HERALD, July 30, 1994).

159. See Kidd, *supra* note 1, at 203.

160. See *id.*

161. See *id.*

162. See Miller, *supra* note 40, at 228-235. (Discussing varying standards in the context of vastly different requirements for informed consent in the U.S., EU, and Japan).

problems for development of a common regulatory scheme.

In the economic sphere, increasing criminal activity, the substantial variation in patent laws worldwide and the subjugation of drug control issues to trade interests, all stand to complicate development of a unified agreement. The lack of laws in the EU regarding re-importation of drug products tends to facilitate introduction of counterfeit drugs into commerce.¹⁶³ This potentially dangerous situation has not yet been dealt with adequately and has required the FDA to incur increased monitoring costs.¹⁶⁴

The lack of consistent patent laws coupled with lack of enforcement of intellectual property rights discourages many manufacturers, both in the U.S. and EU, from expanding their marketing. Overall, this will limit the reach of the MRA.¹⁶⁵

The negotiation of regulatory controls within the framework of general trade agreements may lead to undesired and unintended results. The binding character of trade agreements precludes withdrawal as an option to remedy results which might prove unacceptable *vis a vis* FDA standards.¹⁶⁶

Lastly, the potential for the system to be subverted by exploitation of the economic inequities between countries by diversion of manufacturing to countries with lower wage standards or more permissive approval procedures looms large as a potential problem.¹⁶⁷ The magnitude of return from increasing market share in the world economy is a strong stimulus to find and utilize potential legal loopholes which surely will surface as harmonization progresses. The resulting disruption of an already stressed U.S. health care system by loss of substantial revenues from testing could prove disastrous to medical training which is funded to a great extent by such research grants. With the continuing decline in available funding for health care, the long-term result might be restricted consumer access to the health system with limited options available to those entering the system.

VI. CONCLUSION

There have been some suggestions of progress in movement towards global harmonization.¹⁶⁸ Others have been less optimistic noting that the

163. See 6/1/98 GOLDSHEET, *supra* note 7.

164. See *id.*

165. See generally, Sabatelli, *supra* note 125.

166. See 6/1/98 GOLDSHEET, *supra* note 7.

167. See Alfred C. Aman, Jr., *A Global Perspective On Current Regulatory Reforms: Rejection, Relocation, or Reinvention?* 2 IND. J.GLOBAL LEGAL STUD. 429, 432 (1995).

168. See EMEA 1997 Report: Transition Period Ends, 1/19/1998 MARKETLETTER available in 1998 WL 9220245 (commenting on evaluation of 197 applications by the EMEA in 1997).

diverse factors impacting on the development of a harmonized, international system for drug approval suggest that the end result will somewhat less than the single, controlling entity envisioned by the founders.¹⁶⁹ The results of the effort within the EU will begin to be apparent in 1999. Those results should extrapolate well to the international effort and thus will continue to forecast the problems and results of the combined efforts of the EU, U.S., and Japan.

Realistically, it seems probable that the individual countries will retain ultimate veto power with regard to approval of any single drug or drug product. The real issue is how much will this increase the "dead weight" of regulatory inspections on the international drug industry.¹⁷⁰ If this can be minimized to any extent, the result might be more ready access to drugs in international commerce but with no concomitant lowering of price. On the other hand, if the FDA and Congress continue to view "foreign" efforts with suspicion or distrust, the result would be the opposite - prolongation of approval times, increased costs to the consumer and greater regulatory burden on the drug industry. Economic limitations on governments worldwide are perhaps the trump card in the harmonization effort which will produce a more harmonized, efficient and safe international control mechanism ultimately.

See also, ICH: Phase II Harmonization Begins, 2/23/1998 MARKETLETTER available in 1998 WL 9220534 (noting that two new guidelines are to be implemented, Ethnic Factors in the Acceptability of Foreign Clinical Data and Statistical Principles for Clinical Trials which "will minimize the need to duplicate clinical studies while insuring that safeguards are maintained").

169. *See* Kidd, *supra* note 1, at 204.

170. *Id.* at 206.

