

## AN FDA-EEC PERSPECTIVE ON THE INTERNATIONAL ACCEPTANCE OF FOREIGN CLINICAL DATA

### INTRODUCTION

When Beth and her husband spent the year in London, she found relief from her asthma for the first time in years. Her British doctor prescribed Zaditen (ketotifen),<sup>1</sup> a popular medication that has been available in Europe for many years. When she returned to the U.S., however, Beth was disappointed to learn that Zaditen was not available. In desperation, Beth had friends in England send it to her.

Bill was not so fortunate. He suffered from Parkinson's disease and the medications his doctor had tried were no longer working well. He knew another Parkinson's patient who was in good shape. He was from Austria and his family was sending him Eldepryl (deprenyl).<sup>2</sup> It had been available in Europe since the early 1980s, but it was not approved in the U.S. until 1989, by which time Bill's condition had deteriorated considerably.<sup>3</sup>

Unfortunately, there are many people like Beth and Bill, not only in the United States but around the world, who can't get access to new drugs. Many drugs, which are available in some countries, are not available in others because drug regulatory agencies decide differently in approving or rejecting a new drug for distribution to patients like Beth and Bill.

One of the most important factors a drug regulatory agency must consider in making the decision to approve or reject a new drug is analyzing the data derived from clinical tests on humans which shows if a new drug is safe and effective. Drug regulatory agencies are exacting in their scrutiny of this clinical data<sup>4</sup> because it often determines if a new drug will be approved or rejected for distribution.

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1. Zaditen (ketotifen) is used in the prophylactic treatment of asthma and has also been given in the treatment of allergic conditions such as rhinitis and conjunctivitis.

2. Eldepryl (deprenyl) enhances the effects of levodopa and is used in Parkinson's disease as an adjunct to levodopa therapy, usually when fluctuations in mobility have become a problem. It has also been tried in the treatment of depression.

3. San Diego Tribune, Aug. 24, 1990, at D2, col. 3.

4. Clinical data refers to data derived from any experiment in which a drug is administered to, or used involving, one or more human subjects.

If this clinical data is derived from a foreign source, then the drug regulatory agency treats it even more critically because the data is more difficult to verify and validate. Regulatory authorities often accept a filing but find the foreign clinical data methodologically insufficient, and require the sponsor<sup>5</sup> to re-perform the clinical trials under domestically sanctioned methods at domestic clinical sites. This results in added expense and delay in receiving approval to distribute a new drug.

The purpose of this Comment is to analyze the problems associated with the international acceptance of foreign clinical data, address the current regulations which determine when such data is acceptable, and introduce solutions which will facilitate the pharmaceutical industry in achieving its goal of distributing life saving drugs to patients like Beth and Bill. With this goal of improved health care in mind, this Comment focuses upon two drug regulatory agencies which have recently addressed the subject: the Food and Drug Administration ("FDA") in the United States and the Committee for Proprietary Medicinal Products ("CPMP") in the European Economic Community ("EEC").<sup>6</sup>

First, the background of this controversy is discussed, including some of the problems which inhibit the acceptance of foreign clinical data. Second, FDA policy is assessed with particular attention placed upon the difficulties of non-U.S. clinical investigators meeting FDA requirements such as ethical review, patient informed consent, adherence to the protocol, and general record keeping. Third, the EEC standard for accepting foreign clinical data is analyzed, including a discussion of the various interpretations which have resulted from this standard, as well as a discussion of the steps which have been taken to reduce these varied interpretations. Finally, the barriers inhibiting the international acceptance of foreign clinical data are discussed and specific solutions are proposed to reduce these barriers. These solutions include increasing the methods of communication between regulatory agencies through memorandums of understanding, contract research organizations, and internationalizing assessment reports. Other solutions include reducing economic and political forces and assembling an international drug dossier.

## I. STATEMENT OF THE CONTROVERSY

The pharmaceutical industry has become one of the most regulated industries in the world over the past decade because of its potential to affect such an extraordinary number of people.<sup>7</sup> On the one hand, expansive regulatory

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5. "'Sponsor' means a person who takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization. . . ." 21 C.F.R. § 312.3(b) (1990).

6. The EEC is currently comprised of the following Member States: Belgium, Denmark, France, Greece, Italy, Luxembourg, the Netherlands, Portugal, Spain, the United Kingdom, and Germany.

7. See generally Comment, *International Trends in New Drug Approval Regulation: The Impact on Pharmaceutical Innovation*, 10 RUTGERS COMP. & TECH. L.J. 317, 318-19 (1984).

controls have increased the quality of pharmaceutical drugs reaching the marketplace. On the other hand, however, this increased regulation has caused several problems for the pharmaceutical industry. One of the most troublesome problems which accompanies this increased regulation is "the drug lag"<sup>8</sup> which delays the availability of new drugs to consumers.<sup>9</sup>

Drug regulatory agencies have recognized the problems associated with the drug lag and have attempted to reduce these delays.<sup>10</sup> In doing so, these agencies have recently focused on the acceptance of foreign clinical data.<sup>11</sup> The acceptance of foreign clinical data is important because it involves communication between drug regulatory agencies on an international scale; and "the issue of the communication of drug information is critical because it relates to the very basis of the value of pharmacotherapy in health care: the effective use of drugs depends on the accurate and comprehensive communication and understanding of information about them."<sup>12</sup>

Various drug regulatory agencies have contrasting policies regarding the acceptance of foreign clinical data to support a new drug application or "registration."<sup>13</sup> Typically, the quality of the foreign clinical data is the most important concern for these regulatory agencies because the agency can not easily verify or validate the data since it was performed in a foreign country.

While the quality of the foreign clinical data is certainly a valid concern, acceptance of this data by regulatory authorities is often conditioned on "nationalism" rather than on medical comparability or dissimilarity.<sup>14</sup> National-

8. Cooper, *The Drug Lag*, 37 FOOD DRUG COSM. L.J. 49, 50 (1982); Dunning, *Regulation, New Drug Development, and the Question of Delay*, 41 FOOD DRUG COSM. L.J. 139 (1986).

9. Kaitin, Mattison, Northington & Lasagna, *The Drug Lag: An Update on New Drug Introductions in the United States and in the United Kingdom, 1977 Through 1987*, 46 CLIN. PHARMACOL. & THER. 121, 133-34 (1989).

During the 11-year period from 1977 through 1987, the United States not only lagged behind the United Kingdom in the availability of new medications in each therapeutic category, but it also had only one third the number of first introductions of mutually available drugs and 23% fewer exclusively available drugs. . . . [Kaitin previously] showed that of 46 new chemical entities approved by the FDA in 1985 and 1986, 33 (71.7%) had been marketed in foreign countries a mean of 5.5 years before U.S. approval. Twelve of the 46 new chemical entities had been marketed 6 or more years before U.S. approval. Although one would not expect any country to approve all new drugs first, one would assume that a country such as the United States would not be far down the list a majority of the time.

*Id.*

10. See generally Poggolini, *International Regulation of Drugs*, 22 DRUG INFO. J. 133 (1988); Note, *International Regulation of Pharmaceuticals: The Role of the World Health Organization*, 23 VA. J. INT'L L. 331 (1983); Note, *International Regulation of Pharmaceuticals: A WHO International Code of Conduct for the Marketing of Pharmaceuticals?*, 11 SYRACUSE J. INT'L L. & COM. 121 (1984).

11. O'Reilly, *Three Dimensions of Regulatory Problems: United States, European Economic Community, and National Laws*, 41 FOOD DRUG COSM. L.J. 131, 132 (1986).

12. Hoff, *The Role of the Innovation-Based Pharmaceutical Industry In International Drug Information Communication*, 17 DRUG INFO. J. 271 (1983).

13. Generally, only the FDA terms the new drug submission documents to be an "application." International product submissions are generally termed "new drug registrations."

14. O'Reilly, *supra* note 11, at 132.

ism can be briefly described as one agency's prejudice against another agency's standard for accepting such data.<sup>15</sup> These "excuses" for rejecting foreign data almost always require that repetitive testing be performed domestically so the agency can more closely monitor the study and more easily validate the data.<sup>16</sup>

The effects of repetitive testing can be disastrous in terms of wasted time, money and resources. For instance, finding a foreign testing facility capable of adequately performing the clinical trial is difficult.<sup>17</sup> Additionally, data must be re-prepared and re-organized to support the new drug registration. There is also no guarantee that the data will be considered if a minor or technical mistake was made along the way. Thus, an agency's refusal to accept foreign clinical data, and the subsequent repetitive testing, magnifies the drug lag problem rather than reduces it.

The FDA and CPMP have responded to the problems associated with the international acceptance of foreign clinical data by passing regulations designed to set standards in determining when the data will be acceptable. An examination of these standards is necessary in order to understand the barriers which inhibit, and the solutions to encourage, the acceptance of foreign clinical data.

## II. FDA POLICY

### A. Prominence of the FDA in International Pharmaceutical Regulation

The FDA is the sole national food and drug regulatory agency in the United States. Its authority is derived from the Federal Food Drug and Cosmetic Act.<sup>18</sup> The FDA has long been considered the most prominent drug regulatory agency in the world and has established its position of leadership and prestige in the community of international drug regulatory authorities.<sup>19</sup>

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15. See *infra* notes 167-74 and accompanying text.

16. O'Reilly, *supra* note 11, at 132.

17. See *infra* notes 97-102 and accompanying text.

18. 21 U.S.C. §§ 301, 321, 331-337, 341-469, 347, 348, 351-353, 355-357, 361-363, 371-376, 381, 391, 392 (1990). The original Act was passed in 1906 and has been amended numerous times to clarify the requirements in assuring safe and effective performance of a new drug or medical device.

19. Halperin, *Multinational and International Regulation of Pharmaceuticals and U.S. Policy*, 17 DRUG INFO. J. 153, 154 (1983).

This reputation derives from several facts: 1) The agency is the largest drug regulatory body in the world; it has the broadest [range] of statutes, regulations, guidelines, and formal policies and procedures of any drug regulatory agency. . . . 2) A decision to approve a drug for marketing in the United States—with its population of almost 230 million people—is possibly the single most important action affecting that drug throughout its lifetime because it permits entry into the largest single market in the world. It is a decision virtually equal to approving a drug for a population almost as large as the entire [EEC]. 3) The American democratic system of government places a high value on 'Government in the Sunshine.' . . . It is the most public system of decision making in the world and the amount of information that is available to outside parties for independent review of how the [FDA] exercises its statutory mandate is more extensive than in other countries. 4) Finally, the agency itself takes its responsibilities to the international community seriously and works hard to meet its

Along with this prestige, the FDA must keep up to date with technological advancements. The FDA's acceptance of foreign clinical data can be considered a technological advancement because only recently has the international community used foreign clinical data to support safety and efficacy of a new drug. The FDA's awareness of the need to accept foreign clinical data can be largely attributed to the pressure which private industry has placed upon the FDA.<sup>20</sup>

### B. History of Accepting Foreign Clinical Data

The FDA advised the pharmaceutical industry in 1962 that foreign clinical data meeting the standards of adequate and well-controlled studies would be acceptable.<sup>21</sup> However, the FDA limited the use of this data to that of a literature review,<sup>22</sup> which meant that the data could only be used as supplemental information of the drug's safety and efficacy.

It was not until 1975 that the FDA accepted foreign clinical studies as primary evidence of a drug's safety or efficacy.<sup>23</sup> But even at this time, before the FDA would accept the foreign clinical data, the drug in question must have been for a major health gain, an uncommon disease, or must have had a strikingly favorable benefit/risk ratio.<sup>24</sup>

Certainly the FDA's position has continued to evolve over the years to one of greater acceptance and reliance on foreign studies. In part, this probably reflects some evolution in the design and conduct of clinical studies throughout the world, and the submission of higher quality clinical data. As scientific standards for the clinical study of drugs gain wider acceptance throughout the world, unnecessary duplication of clinical studies becomes more clearly unjustifiable.<sup>25</sup>

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commitments and maintain our reputation.

*Id.*

20. Lisook & Sloboda, *Food and Drug Administration Audit of Foreign Clinical Trials*, 23 PSYCHOPHARMACOLOGY BULL. 193 (1987).

21. Bilstad, *Foreign Clinical Data: FDA Perspective*, Paper presented to the Fifth International Meeting of Pharmaceutical Physicians, Munich, Federal Republic of Germany (Oct. 1984) (available from Dr. Bilstad, Dept. of Health and Human Services, HFD-500, Public Health Service, Food and Drug Administration, Rockville, MD, 20857).

22. Lisook & Sloboda, *supra* note 20 (citing Weintraub, *Foreign Data: 1986 Status*, Paper presented to the 10th Annual Meeting of the Associates of Clinical Pharmacology, San Francisco, Cal. (Apr. 1986)).

23. Lisook, *FDA Investigation of Clinical Studies: Policy and Procedure*, Paper presented at the Third Annual European Symposium, Good Clinical Practice in Europe, Copenhagen, Denmark, at 14 (Mar. 3, 1989) (Dr. Lisook, who generously provided this article, is currently Chief of the Clinical Investigations Branch, Division of Scientific Investigations, HFD-344, Office of Compliance, Center for Drug Evaluation and Research, Food and Drug Administration, Rockville, MD, 20857).

24. *Id.* at 15.

25. Bilstad, *supra* note 21, at 1.

Finally, in 1984, under pressure from foreign governments, pharmaceutical companies, and academic and consumer groups, the FDA formally restated its policy towards accepting foreign clinical data.<sup>26</sup>

### C. Current Policy

The FDA has recognized two categories concerning the acceptability of foreign clinical data. These categories, discussed in more detail below, are: 1) foreign clinical studies not conducted under an investigational new drug application<sup>27</sup> ("IND"), and 2) marketing approval based solely on foreign clinical data. Once these regulations have been presented, a brief comparison of their applicability is discussed.

1. *Foreign Clinical Studies Not Conducted Under an IND.* In general, FDA accepts foreign clinical studies not conducted under an IND if the studies are "well designed, well conducted, performed by qualified investigators,<sup>28</sup> and conducted in accordance with ethical principles acceptable to the world community."<sup>29</sup> Studies meeting these criteria may be used to support clinical investigations<sup>30</sup> and/or marketing approval in the United States.<sup>31</sup> A sponsor who wishes to rely on foreign clinical studies to support an IND<sup>32</sup> or to support a new drug application ("NDA")<sup>33</sup> must submit the following information to the FDA:<sup>34</sup>

- (1) A description of the investigator's qualifications;
- (2) A description of the research facilities;
- (3) A detailed summary of the protocol and results of the study, and, should FDA request, case records maintained by the investigator or

26. Lisook & Sloboda, *supra* note 20, at 193.

27. An investigational new drug exemption refers to a scientific document submitted to and reviewed by the FDA. The new drug is one which the FDA has not yet approved for marketing distribution and can only be placed in interstate commerce for the purpose of scientific investigation. Investigational new drug is defined as "a new drug, antibiotic drug, or biological drug that is used in a clinical investigation. The terms also includes a biological product that is used in vitro for diagnostic purposes." 21 C.F.R. § 312.3(b) (1990).

28. "'Investigator' means an individual who actually conducts a clinical investigation (i.e., under whose immediate direction the drug is administered or dispensed to a subject). . . ." 21 C.F.R. § 312.3(b) (1990).

29. 21 C.F.R. § 312.120(a) (1990).

30. "'Clinical investigation' means any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects." 21 C.F.R. § 312.3(b) (1990).

31. 21 C.F.R. § 312.120(a) (1990).

32. For the IND regulations, *see* 21 C.F.R. § 312 (1990). Part 312 describes the general provisions governing the IND application (§§ 312.1-312.10), the IND application procedure (§§ 312.20-312.28), administrative actions (§§ 312.40-312.48), responsibilities of sponsors and investigators (§§ 312.50-312.70), drugs intended to treat life-threatening and severely-debilitating illnesses (§§ 312.80-312.88), miscellaneous provisions (§§ 312.110-312.145).

33. FDA has codified the new drug application procedure at 21 C.F.R. § 314 (1990).

34. 21 C.F.R. § 312.120(b) (1990).

additional background data such as hospital or other institutional records;

(4) A description of the drug substance and drug product used in the study, including a description of components, formulation, specifications and bioavailability of the specific drug product used in the clinical study, if available; and

(5) If the study is intended to support the effectiveness of a drug product, information showing that the study is adequate and well controlled under § 314.126.<sup>35</sup>

Furthermore, the sponsor must conform with ethical principles as stated in the Declaration of Helsinki.<sup>36</sup> The FDA has adopted certain provisions of the Declaration because it is considered the most modern international instrument in dealing with medical research.<sup>37</sup>

2. *Marketing Approval Based Solely on Foreign Clinical Data.* The FDA has also promulgated standards under which foreign clinical data can be used as the sole basis for marketing approval.<sup>38</sup> A new drug based solely on foreign clinical data may be approved if:

(1) The foreign clinical data are applicable to U.S. population and U.S. medical practice;

(2) The studies have been performed by clinical investigators of recognized competence; and

(3) The data may be considered valid without the need for an on-site inspection by FDA or, if FDA considers such an inspection to be necessary, FDA is able to validate the data through an on-site inspection or other appropriate means.<sup>39</sup>

If an application fails to meet any of these criteria, it will not be approved on

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35. 21 C.F.R. § 312.120(b) (1990).

36. 21 C.F.R. § 312.120(c) (1990). Such an example of an ethical principle is found in the Declaration of Helsinki § III(4) which states that "[i]n research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject," reprinted in 21 C.F.R. § 312.120(c)(4) (1990).

37. Deutsch, *Medical Experimentation: International Rules and Practice*, 19 VICT. U. WELL. L.R. 1, 7 (1990).

[The Declaration] is universally accepted because it makes the necessary distinction between therapeutic research and purely scientific experimentation; it insists on a medically acceptable benefit-risk ratio; it requires the informed consent of the subject; it installs ethical committees, and finally it requires publishers of learned journals to assess the ethical propriety of medical research papers submitted.

*Id.*

38. 21 C.F.R. § 314.106 (1990).

39. *Id.*

the foreign clinical data alone.<sup>40</sup> However, the FDA is flexible and encourages applicants to meet with agency officials in a "presubmission" meeting when approval is based solely on foreign clinical data.<sup>41</sup>

The three criteria listed immediately above are only relevant if a foreign clinical trial is pivotal for FDA approval (for example, one of only two clinical trials showing effectiveness).<sup>42</sup> If U.S. data exists which is convincing per se, and foreign trials confirm the U.S. data, then FDA is not overly concerned about the foreign data.<sup>43</sup> In other words, the acceptance of foreign trials as evidence of a drug's effectiveness is primarily a problem where the data is essential for U.S. approval.<sup>44</sup>

3. *Comparing the FDA Standards.* The FDA's policy in accepting foreign clinical data is not affected by the regulation under which the sponsor decides to submit the data.<sup>45</sup> In both of the aforementioned regulations, the FDA typically treats the foreign clinical data the same.<sup>46</sup> The reason there are different sets of regulations is because the foreign data will be assessed at different times during the application process. For example, if an IND application is not held up by the FDA, the sponsor is authorized to perform clinical trials involving the new drug.<sup>47</sup> However, the sponsor must still follow the NDA procedure before the drug will be approved for marketing distribution.<sup>48</sup> This NDA must include any data which the FDA originally assessed in granting the IND application to the sponsor. As a result, the FDA can track the history of the drug through the application process and can determine if and when the foreign clinical data was originally assessed.

Additionally, there is one unstated difference that the FDA applies between the regulations. When the FDA receives an application involving foreign data, they often conduct an investigation of the location where the data was derived.<sup>49</sup> The FDA usually classifies these either as "routine" investigations or "for-cause" investigations.<sup>50</sup> The routine investigation does not require participation by FDA headquarters staff personnel at the study site, and is generally accomplished

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40. *Id.*

41. *Id.*

42. Lasagna, *On Reducing Waste in Foreign Clinical Trials and Postregulation Experience*, 40 CLIN. PHARMACOL. & THER. 369, 370 (1986).

43. *Id.*

44. *Id.*

45. Telephone interview with Dr. Alan Lisook, Chief of the Clinical Investigations Branch, Division of Scientific Investigations, Office of Compliance, Center for Drug Evaluation & Research, Food and Drug Administration (Sept. 11, 1990).

46. *Id.*

47. See *supra* notes 27-35 and accompanying text.

48. See *supra* note 33 and accompanying text.

49. See Lisook, *supra* note 23. See also P. Smith, FDA's International Regulatory Role Through the Foreign Inspection Program (Sept. 1990) (available from Arthur A. Checchi, Inc., (292) 452-8666, Document I.D. No. 001-0133).

50. Telephone interview, *supra* note 45. See also Lisook, *supra* note 23.



with an FDA field investigator and the clinical investigator, not the sponsor.<sup>51</sup> A for-cause investigation generally involves an FDA investigator and the participation of a member of FDA headquarters staff at the study site.<sup>52</sup> The FDA usually classifies foreign studies as for-cause investigations only because the foreign data is pivotal for FDA approval.<sup>53</sup> The important aspect to keep in mind is that, by following the regulatory requirements outlined above, a sponsor can reduce the delays associated with receiving FDA approval.

4. *Examples of Approved Drugs Based Upon Foreign Clinical Data.* Only recently and in rare circumstances has FDA granted approval for new drugs based upon foreign clinical data. "The timolol<sup>54</sup> clinical study conducted in Norway was a historic first, the first drug accepted by FDA on the basis of solely non-U.S. clinical testing."<sup>55</sup> Besides timolol, only three other drugs based solely on non-U.S. clinical studies have been approved by the FDA: Mesnex,<sup>56</sup> Haldol

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51. Telephone interview, *supra* note 45. Under the routine inspection program, approximately 200-250 inspections of clinical investigations per year are performed in the drug area. The inspections are limited in scope and are conducted by members of an FDA field staff. The assignments are issued as needed and are based almost exclusively on studies which are deemed important to the evaluation of new drug applications pending before the agency. With certain exceptions, important studies in every NDA which contains clinical data are the subject of such inspections. Lisook, *supra* note 23, at 3.

52. Telephone interview, *supra* note 45. The reasons for the initiation of such "for-cause" inspections are diverse. Although they are termed "for-cause" inspections, this does not necessarily mean that information exists which would lead one to believe that work was done improperly. An inspection of a clinical investigator may be initiated because: 1) they are doing a large volume of work; 2) they have done work outside their field of specialty; 3) they report efficacy for a drug which appears to be too good when compared with the results of other physicians studying the same drug; 4) they report no toxicity or few adverse reactions when other physicians report numerous adverse reactions; 5) they seem to have too many patients with a given disease for the locale where they practice; 6) they report laboratory results which are consistent beyond usual biologic variation or which are inconsistent with results submitted by other investigators; 7) representatives of the sponsor have reported that they are having difficulty getting case reports from the investigator; 8) a subject of a study complains to FDA about violations of the protocol or the patient's rights; 9) they have done a truly pivotal piece of work which merits in-depth examination because of its importance. *This includes all foreign studies which are primary evidence in support of U.S. drug approval*; 10) they have done a study which draws significant media attention. Lisook, *supra* note 23, at 8-9 (emphasis added).

53. Telephone interview, *supra* note 45. Once it has been determined that a "for-cause" inspection is to take place, arrangements are made with the clinical investigator. Procedures used are essentially the same as in the routine inspections, except that the data audit goes into greater depth, covers a larger number of individual case reports, and may, as indicated, cover more than one study. If deficiencies are found which indicate that the investigator has repeatedly or deliberately violated FDA regulations, or has submitted false information to the sponsor in a required report, then FDA will initiate actions which may ultimately result in the determination that the clinical investigator not receive investigational new drugs in the future. Lisook, *supra* note 23, at 10. *See also* O'Reilly, *More Gold and More Fleece: Improving the Legal Sanctions Against Medical Research Fraud*, 42 ADMIN. L. REV. 393 (1990).

54. Timolol has been shown to be effective in preventing myocardial re-infarction. It has also been effective in lowering intraocular pressure and may be indicated in patients with chronic open-angle glaucoma or glaucoma in aphakic eyes.

55. O'Reilly, *supra* note 11, at 132 n.7.

56. Mesnex has been shown to be effective as a prophylactic agent in reducing the incidence of ifosfamide induced hemorrhagic cystitis.

depot,<sup>57</sup> and Cyclokapron.<sup>58</sup>

Other drugs where foreign clinical data has been pivotal in achieving FDA approval are cimetidine,<sup>59</sup> nifedipine for vasospastic angina,<sup>60</sup> several oncologic<sup>61</sup> drugs, and a radio-pharmaceutical<sup>62</sup> drug.<sup>63</sup> Examples of new drugs approved based on a combination of U.S. and non-U.S. studies include Marinol,<sup>64</sup> Buspar,<sup>65</sup> Nolvadex,<sup>66</sup> Losec,<sup>67</sup> and Nimotop.<sup>68</sup>

An example of where a United Kingdom license was granted entirely on the basis of clinical data generated outside the U.K. is Azidothymidine ("AZT").<sup>69</sup> The license was granted entirely on the basis of clinical data from the U.S.<sup>70</sup>

Hopefully, such grants of approval based solely on foreign clinical data will occur more frequently so that new drugs can reach patients sooner. The fact that some drugs have been approved in the U.S. with the use of foreign clinical data suggests that FDA is pushing toward this goal. However, for FDA to accept future foreign clinical studies, private industry must be aware of certain difficulties in meeting FDA requirements so that repetitive clinical trials can be avoided.

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57. Haldol (haloperidol) is indicated for use in the management of manifestations of psychotic disorders. It is also indicated for the control of tics and vocal utterances of Tourette's disorder in children and adults.

58. Cyclokapron (Tranexamic acid) is indicated for the management of hemophilic patients undergoing tooth extraction or other oral surgical procedures.

59. Cimetidine inhibits gastric secretion of hydrochloric acid by all stimuli and is a frequently used medication for the treatment of peptic ulcers.

60. Nifedipine (Procardia) is indicated for the management of vasospastic angina. It regularly reduces arterial pressure at rest and at a given level of exercise by dilating peripheral arterioles and reducing the total peripheral resistance against which the heart works. This unloading of the heart reduces myocardial energy consumption and oxygen requirements.

61. Oncologic drugs help in the destruction of tumors in human patients.

62. A diagnostic radiopharmaceutical drug is one which is tagged with a radionuclide so that its course can be traced, measured, or imaged.

63. Lasagna, *supra* note 42, at 369.

64. Marinol is indicated for the treatment of the nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments.

65. Buspar (Buspirone HCL) is an anxiolytic which is indicated for the treatment of anxiety disorders. Buspar is clinically effective for the management of anxiety disorders or the short-term relief of symptoms of anxiety.

66. Nolvadex is effective in the treatment of metastatic breast cancer in women.

67. Losec (Omeprazole) is a drug which decreases gastric acid production; it is used in the treatment of Zollinger-Ellison syndrome and in gastro-esophageal reflux disease.

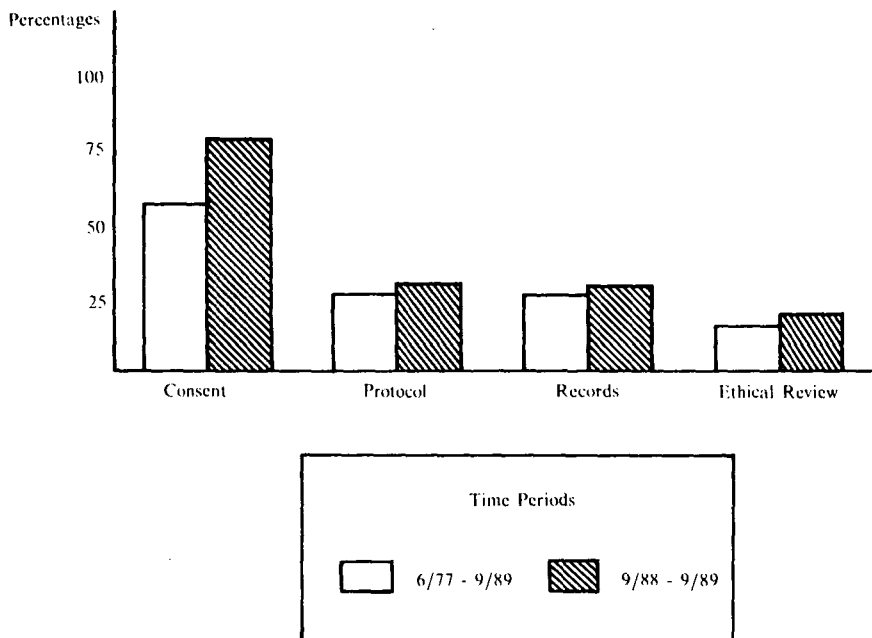
68. Nimotop is indicated for the improvement of neurological deficits due to spasm following subarachnoid hemorrhage from ruptured congenital intracranial aneurysms in patients who are in good neurological condition post-ictus.

69. AZT (Azidothymidine or Zidovudine) is indicated as a primary agent in the treatment of selected patients with symptomatic acquired immunodeficiency syndrome ("AIDS"). Zidovudine is not a cure for AIDS.

70. Jones, *Acceptance of Foreign Clinical Data*, 22 DRUG INFO. J. 95, 96 (1988).

### D. Difficulties in Meeting FDA Requirements

A sponsor, when proffering foreign clinical data to the FDA, must be aware of certain difficulties in meeting the regulatory requirements. These difficulties most often arise in the areas of: 1) ethical review, 2) patient informed consent, 3) adherence to the protocol, and 4) access to clinical records for inspection purposes.<sup>71</sup> These four categories are called difficulties because they can often be the reason an FDA official decides to reject a particular foreign study.



206 inspections 9/88 - 9/89  
 2261 inspections 6/77 - 9/89

71. See generally Honohan, *Practical Problems in the Conduct of Non-US Studies from Which Data Will Be Used for US Registration*, 22 DRUG INFO. J. 193 (1988); Lisook, *supra* note 23.

The FDA recently has tabulated data about the most common deficiencies found in domestic studies.<sup>72</sup> The preceding graph shows that from June 1977 to September 1989 the FDA conducted more than 2,000 investigations in the drug area. Of these investigations, the graph shows the most common problems associated with the performance of these studies.<sup>73</sup>

1. *Ethical Review.* The Declaration of Helsinki<sup>74</sup> requires that an ethical review committee<sup>75</sup> must examine a sponsor's procedures before undertaking a clinical trial. This requirement poses a problem if a committee is not available at the study site for an independent review. In such a case, the sponsor must demand that some type of ethical review be made available before the study begins. For example, a "for profit" committee can be used to review the protocol and maintain review of the study, or the sponsor can assist in the formulation of an ethical review committee to review the protocol.<sup>76</sup> At a minimum, FDA requires that the sponsor submit the names and qualifications of the committee's members<sup>77</sup> in order to determine that a review committee in fact existed.

2. *Patient Informed Consent.* The investigator has the responsibility of

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72. Lisook, *supra* note 23. For another recent study, see Food and Drug Administration, New Molecular Entities Submitted in 1984-85: Analysis of Review Cycles, Amendments and Deficiencies (Dec. 1988) (Evaluation and Analysis Staff, Office of Planning and Evaluation, Food and Drug Administration, Rockville, MD, 20857).

73. Lisook, *supra* note 23, at 5-6 and figure 2. The graph requires some explanation. Since an investigation may find multiple deficiencies or no deficiencies, the total percentages noted will not equal 100. The 52% on problems with patient informed consent is not surprising since this figure encompasses *all* instances where it was deemed necessary to make some comment to the investigator concerning things which he included in the consent form which should not have been included, or where something which should have been included was not. It was only the rare instance where required consent was not obtained. *The deviations from protocol, the records' inaccuracy and records' non-availability are of more concern. These are the figures which cast doubt upon the validity of the studies audited. It is this kind of problem which may cause the FDA to take a closer look at the clinical investigator.* *Id.* (emphasis added).

74. The Declaration of Helsinki, § I(2), requires that "[t]he design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted to a specially appointed independent committee for consideration, comment and guidance," *reprinted in* 21 C.F.R. § 312.120(c)(4) (1990).

75. An ethical review committee is an independent body whose responsibility is to verify that the rights and integrity of humans in a particular study are protected, thereby providing public assurances. The requirement that an ethical review committee exist to review the investigators procedures and practices can be explained as follows:

Most scientists are under great pressure to conduct research and publish it. Publication is the sole route to professional success, to salary increases, to tenure, to promotion. Scientists, therefore, regard the terms and conditions of publication as matters of considerable importance. There is no question that ethical review as a gate to publication is an effective means of maintaining ethical standards in research. It is also the most feasible method.

R. LEVINE, ETHICS AND REGULATION OF CLINICAL RESEARCH 19 (1981).

76. Honohan, *supra* note 71, at 194.

77. 21 C.F.R. § 312.120(c)(3) (1990).

obtaining written and signed patient informed consent<sup>78</sup> before the clinical study begins.<sup>79</sup> When a particular country or institution does not regularly require signed patient consent forms, such assurances should be agreed upon between the sponsor and the investigator before the study begins.<sup>80</sup>

Two other alternatives can be used to satisfy the patient informed consent requirement. A witness attestation form can be used where a witness signs the consent form attesting to the fact that the patient was accurately informed.<sup>81</sup> In the alternative, the investigator can sign a witness attestation form confirming the fact that the patient received adequate information about the testing involved.<sup>82</sup> However, these methods are questionable when seeking FDA approval because FDA requires patient informed consent to be in writing. Therefore, if signed patient informed consent is not obtained, it is possible that FDA may reject the entire study because there is no documentation that the patient was adequately informed of the risks involved in participating in the experiment, as required by the Declaration of Helsinki.

3. *Protocol Non-Adherence.* One of the most commonly encountered circumstances which leads FDA to recommend the rejection of a particular foreign study is the failure of the investigator to follow the protocol.<sup>83</sup> There are numerous ways that an investigator can deviate from the protocol which causes the FDA to be concerned. For example, misreporting the duration of drug therapy and/or drug dosage; misreporting duration of disease remission by using dates of office visits rather than reoccurrence of symptomology which might have been weeks earlier; using ineligible subjects such as those with minimal disease, undocumented disease, or with the wrong disease; and, finally, the study may not have been double-blind as was required.<sup>84</sup>

Such deviations from protocol are of great concern to the FDA when

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78. The following dialogue serves as an example of the principle of patient informed consent:

Investigator (I): "Before we treat Mr. Jones with investigational drug X, we tell him that drugs Y and Z are also likely to be effective for his condition." (Judgment).

Colleague (C): "Why *should* we tell him that?"

I: "Because the regulations state that we may not proceed without informed consent, of which one essential component is a disclosure of any appropriate alternative procedures that might be advantageous." (Rule).

C: "Why was that rule promulgated?"

I: "It is designed to be responsive to the principle of *respect for persons*, which requires that we treat individuals as autonomous agents. Persons cannot be fully autonomous without an awareness of the full range of options available to them." (Principle).

R. LEVINE, *supra* note 75, at 9.

79. Declaration of Helsinki § I(9), *reprinted in* 21 C.F.R. § 312.120(c)(4) (1990).

80. Honohan, *supra* note 71, at 194.

81. *Id.*

82. *Id.*

83. Lisook, *supra* note 23, at 18.

84. *Id.*

reviewing the practices of the investigator.<sup>85</sup> These deviations, when they occur, cast doubt on the validity of the studies audited.<sup>86</sup> It is this kind of problem that may cause FDA to reject a study as invalid and which may cause FDA to look more closely at the clinical investigator.<sup>87</sup> Therefore, it is of paramount importance to follow the protocol as designed, or, in the alternative, to obtain the proper approval by the ethical review committee *and* the consent of the patient before deviating from the protocol.

4. *Access to Clinical Records.* Before the FDA will accept foreign clinical data, they must be granted the opportunity to audit the study records.<sup>88</sup> This can be a problem because some countries have legal restrictions denying access to medical records.<sup>89</sup> The laws are designed to keep patient information confidential.<sup>90</sup>

Before the clinical study begins, an agreement must be made which would allow FDA access to clinical records. A common practice is to have the auditor sit with his case report forms on one side of a table, and the investigator with the patient records on the other.<sup>91</sup> This enables the investigator to immediately answer any questions the auditor might pose.<sup>92</sup> This approach, however, even though acceptable by some regulatory agencies, is *not* acceptable to FDA. FDA *must* have access to the patient records.<sup>93</sup> The sponsor must therefore inquire into any such legal restrictions *before* undertaking the study.

In sum, by taking these problems into consideration before foreign clinical trials are initiated, the sponsor can assure FDA officials that the protocol was strictly adhered to and that regulatory requirements have been met. When a sponsor conducts a foreign clinical trial and submits the data to the FDA, the FDA must be satisfied that an ethical review board existed, that the patients were adequately informed, that the protocol was accurately followed, and that clinical records are accurate and are available for inspection. If FDA finds that these components exist, they are more inclined to accept the data because it has met the regulatory requirements.

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85. *Id.* at 6.

86. *Id.*

87. *Id.* When an FDA investigator discovers such a problem as a deviation from protocol, two courses of action are open. The first is an expanded inspection covering the study which is currently being audited. This is accomplished by sending additional case reports to the field. The second course of action is to complete the inspection on the basis of the case reports already reviewed and to initiate a "for cause" inspection in the near future to cover additional cases from the same study as well as other studies which the clinical investigator has recently completed. *See supra* notes 49-53 and accompanying text. Lisook, *supra* note 23, at 6-7.

88. 21 C.F.R. § 314.106 (1990).

89. Honohan, *supra* note 71, at 195.

90. *Id.*

91. *Id.* at 196.

92. *Id.*

93. Telephone interview, *supra* note 45.

### E. *Alternative Means of Qualifying Foreign Clinical Data*

The FDA recognizes two other methods of facilitating the acceptability of foreign clinical data. These are Memorandums of Understanding ("MOUs") and Contract Research Organizations ("CROs"). These methods are important because they open up international channels of communication, both in private industry and between regulatory agencies, which may ultimately result in the increased acceptability of foreign clinical data.

1. *Memorandums of Understanding.* A Memorandum of Understanding is an agreement involving an exchange of information between two drug regulatory agencies. MOUs provide for an exchange of inspection report results, an evaluation of the reports by the authority requesting the inspection, and the reciprocal or joint use of inspectors.<sup>94</sup>

MOUs, once executed between the U.S. and a foreign country, establish the legal basis for FDA reliance upon inspections of *pre*-clinical laboratories and pharmaceutical manufacturing plants conducted by foreign inspectors.<sup>95</sup> FDA is willing to accept studies received from those foreign laboratories based on the inspections performed, and assurances given, by the foreign drug regulatory agency.

However, there are two problems associated with MOUs. The first is that there are no MOUs in the clinical inspection area; none have even been discussed.<sup>96</sup> The second problem with MOUs relates to their enforcement. Since an MOU is technically an agreement rather than a contract, the parties must act in good faith to honor their promises when conducting inspections and recording their results. Assuming that this good faith requirement will be upheld, MOUs are one of the most important ways to increase the acceptability of foreign *clinical* data because agencies share information about regulatory requirements and particular pharmaceutical manufacturers. Hopefully, if such MOUs continue their success at the *pre*-clinical level, this can foster a relationship between the regulatory agencies to open the door to future discussions on an MOU program for clinical studies.

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94. Buday, *Worldwide Drug Regulatory Controls—Are They/Will They Become Uniform?*, DRUG INFO. J. 47, 52 (Apr.-June 1980). See also Halperin, *supra* note 19, at 160. FDA has executed MOUs with Switzerland, Sweden and Canada for mutual acceptance of Good Manufacturing Practice inspections. Similarly, FDA has MOUs covering Good Laboratory Practice inspections with Switzerland, Sweden, Canada, and Japan. FDA annually meets with representatives of the Canadian Health Protection Branch and the U.K. Department of Health and Social Security to discuss problems covering all aspects of agency programs including foods, drugs, cosmetics and medical devices. In addition to Canada and the U.K., FDA holds individual bilateral meetings with a number of countries including Italy, Sweden, Hungary, Israel, Egypt, Finland, Brazil, and Japan.

95. The FDA also maintains its own foreign inspection activities, sending inspectors to drug manufacturing plants all over the world to determine whether or not products they produce are suitable for import into the U.S. See Lisook, *supra* note 23.

96. Telephone interview, *supra* note 45.

2. *Contract Research Organizations.* A CRO is a corporation which acts as an independent contractor to perform clinical studies on behalf of the sponsor.<sup>97</sup> CROs are useful because they allow a sponsor to accomplish demanding clinical research programs without the need for an internal short term increase in staff.<sup>98</sup> CROs design drug study protocols, locate and hire clinical investigators to perform the studies, prepare and send the required patient evaluation and reporting forms to the clinical investigators, monitor the studies for the sponsor, tabulate the data that is compiled, and prepare the final reports for the sponsor.<sup>99</sup>

Before a CRO is actually employed, the sponsor must qualify the CRO to determine if it is capable of performing the study.<sup>100</sup> For example, prior to the instigation of the study, the CRO must be able to identify, qualify and approve investigators, inspect and qualify clinical laboratories, assist with independent review boards or ethics committee review, audit the progress of the study, and allow periodic monitoring of reports.<sup>101</sup> The single most important factor to ensure satisfactory CRO performance is to examine the CRO's management supervision of the people who actually do the day-to-day work, because workers will rarely deliver a better quality product than management demands.<sup>102</sup>

If the foreign clinical studies are adequately prepared by the sponsor and the CRO, the FDA may be more willing to accept future studies. Once the FDA becomes familiar with particular CROs, they may be more willing to accept a study from a foreign corporation using a reputable CRO.

By reviewing the foregoing sections, it is apparent that the FDA has expended considerable effort in establishing standards for accepting foreign clinical data. Similarly, the EEC has attempted to facilitate the use and acceptability of foreign clinical data.

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97. "'Contract research organization' means a person that assumes, as an independent contractor with the sponsor, one or more of the obligations of a sponsor, e.g., design of a protocol, selection or monitoring of investigations, evaluation of reports, and preparation of materials to be submitted to the Food and Drug Administration." 21 C.F.R. § 312.3 (1990).

98. Sewell, *Identification and Qualification of Foreign Contract Research Organizations*, 22 DRUG INFO. J. 173 (1988).

99. *Leo Winter Assoc., Inc. v. Dep't of Health & Human Services*, 497 F. Supp. 429, 431 (D.C. Cir. 1980). The District Court held that a contract research organization is subject to the regulatory controls imposed by FDA "[b]ecause [the CRO] has assumed the technical responsibility placed upon manufacturers and sponsors, [and because] it has also assumed the obligations imposed on sponsors by the Act, and subjected itself to investigations authorized by the [Act]. Any conclusion to the contrary would subvert the remedial purposes of the legislation and significantly undermine its effectiveness." *Id.*

100. Sewell, *supra* note 98, at 174-75. The various pitfalls which the sponsor must address are the location of a CRO; method of contacting the CRO; IND status; delegation of responsibilities for the CRO; time frames; contract requirements; IRB/Ethics committee review; informed consent; source document review; standard operating procedures; drug accountability; adverse events reporting; and monitoring reports.

101. *Id.*

102. *Id.*



### III. EEC POLICY

#### A. EEC Legislation

The EEC was established in 1957 under the Treaty of Rome which clearly defined its aim as the free movement of goods and services between its Member States.<sup>103</sup> The Treaty was designed to promote a harmonious development of economic activities between the Member States belonging to the Community.<sup>104</sup> The Treaty was also designed to promote a continuous and balanced expansion, an increase in stability, a higher standard of living, and closer relations between the Member States.<sup>105</sup>

One of the categories of goods and services affected by this free movement ideology is the pharmaceutical industry. The EEC Commission<sup>106</sup> has adopted numerous regulations regarding the sale and approval of new drugs and pharmaceutical chemicals among the Member States to increase available health care to its citizens and to reduce trade barriers within the Community.<sup>107</sup> An examination of these standards is necessary in order to understand the barriers which inhibit, and the solutions to encourage, the acceptance of foreign clinical data.

#### B. Regulation of Proprietary Medicinal Products

The EEC Commission has passed numerous Directives<sup>108</sup> which regulate the sale and approval of proprietary medicinal products<sup>109</sup> within the Community.

103. P. KAPTEYN & P.V. VAN THEMAAT, INTRODUCTION TO THE LAW OF THE EUROPEAN COMMUNITIES 15 (1973).

104. G. MYLES, 1 EEC BRIEF, Legal Order, ¶ 11 (Supp. 1986).

105. *Id.*

106. Subject to Article 157 of the EEC Treaty, the Commission consists of at least one, but no more than two, members having the nationality of the Member States. It has been agreed that the larger Member States (Germany, Spain, France, Italy and the United Kingdom) should have two Commissioners and the seven smaller Member States should have one Commissioner. See G. MYLES, *supra* note 104, Commission, ¶ 05.

107. For a list of the Community regulations relating to proprietary medicinal products, see The Rules Governing Medicinal Products for Human Use, *infra* note 109, at table of contents.

108. A Directive is secondary Community law which "shall be binding, as to the result achieved, upon each Member State to which it is addressed but shall leave to the national authorities the choice of form and method." EEC Treaty, art. 189, *reprinted in* G. MYLES, *supra* note 104, Legal Order, ¶ 17.

109. A proprietary medicinal product is "any ready-prepared medicinal product placed on the market under a special name and in a special pack." Medicinal product is defined as

any substance or combination of substances presented for treating or preventing disease in human beings or animals. Any substance or combination of substances which may be administered to human beings or animals with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in human beings or in animals is likewise considered a medicinal product.

The primary purpose of these rules is to safeguard the public health.<sup>110</sup> However, in establishing such rules, consideration must be given to the pharmaceutical industry so that research and trade in medicinal products is not hindered.<sup>111</sup>

1. *EEC Standard for Accepting Foreign Clinical Data.* In order to achieve a balance between the public health and the promotion of medicinal products within the Community, the original 1965 standard ("65/65/EEC") for accepting clinical data offered to support a marketing authorization was broad: "The sole criteria which may be taken into consideration by the Member States during the examination of an application for authorization are the quality, safety and efficacy of the product concerned."<sup>112</sup> Additionally, 65/65/EEC states that the marketing authorization "shall be refused if . . . it"<sup>113</sup> proves that the proprietary medicinal product is harmful in the normal conditions of use, or that its therapeutic efficacy is lacking or is insufficiently substantiated by the applicant, or that its qualitative or quantitative composition is not as declared."<sup>114</sup>

This broad language has created problems, however. Since the 65/65/EEC standard is so broad, Member States interpret the criteria differently, which leads to various results concerning the same clinical data.<sup>115</sup>

2. *Problems with Interpreting the EEC Standard.* Due to the broad scope of 65/65/EEC for accepting clinical data, interpretational problems have arisen, particularly when the standard is applied to foreign clinical data. Interpretational conflicts occur because, although all the Member States use the same standard

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O.J. EUR. COMM. (No. L 22) 369 (1965) [hereinafter 65/65/EEC], reprinted in COMMISSION OF THE EUROPEAN COMMUNITIES, I THE RULES GOVERNING MEDICINAL PRODUCTS IN THE EUROPEAN COMMUNITY 23 (1989) (The Rules Governing Medicinal Products for Human Use in the European Community) [hereinafter The Rules Governing Medicinal Products for Human Use].

This five volume set of materials is the *most helpful* information to put all of the EEC regulations into perspective regarding the approval and distribution of medicinal products. Volume I, cited above, is entitled The Rules Governing Medicinal Products for Human Use in the European Community; Volume II is entitled Notice to Applicants for Marketing Authorizations for Medicinal Products for Human Use in the Member States of the European Community; Volume III is entitled The Guidelines on the Quality, Safety and Efficacy of Medicinal Products for Human Use; Volume IV is the Guide to Good Manufacturing Practices for the Manufacture of Medicinal Products; and Volume V is The Rules Governing Medicinal Products for Veterinary Use in the European Community.

110. *Id.*

111. *Id.*

112. 65/65/EEC at 369, reprinted in The Rules Governing Medicinal Products for Human Use, *supra* note 109, at 8.

113. "It" refers to the regulatory authority which rendered a decision on an application for marketing authorization. In accordance with Article 12 of Directive 65/65/EEC, all decisions rendered by the Member States in granting a marketing authorization must be published. The name and address of the Official Journal in each Member State can be found in the Notice to Applicants, *infra* note 123, at 6.

114. 65/65/EEC, reprinted in The Rules Governing Medicinal Products for Human Use, *supra* note 109, at 27.

115. The Rules Governing Medicinal Products for Human Use, *supra* note 109, at 9.

in accepting foreign clinical data, different opinions are reached on the same pre-clinical or clinical data.<sup>116</sup> Opinions differ because regulatory authorities are often influenced by the historical background or past practice of the Member State from where the data was received, rather than the quality of the data itself.<sup>117</sup> Moreover, "due to national differences in medical schools, the harmonization of procedures does not ensure that the results of the standardized procedures are similarly evaluated."<sup>118</sup>

In order to reduce the different opinions being reached by the Member States on the same clinical data, in 1977 the EEC Commission handed down 75/319/EEC which created a Committee for Proprietary Medicinal Products<sup>119</sup> ("CPMP") to assist the Member States in developing a consistent interpretation of the EEC standard. The CPMP's goal is to achieve a balance between the considerations of public health and the promotion of medicinal products within the Community.<sup>120</sup> The purpose of the CPMP is to facilitate the adoption of a common position by the Member States regarding the approval of marketing authorizations for new medicinal products.<sup>121</sup> Adopting a common position would promote the free movement of proprietary medicinal products within the Community and would provide patients with improved access to new drugs.<sup>122</sup>

### C. Resolution of Differing Opinions

The CPMP, in order to reduce the different opinions rendered by the Member States on the same clinical data, recently created three methods which help interpret the 65/65/EEC standards. These methods consist of a new set of application guidelines known as the "Notice to Applicants," the use of updated information packets known as "assessment reports," and a Note for Guidance prepared by the CPMP Working Party on Efficacy of Medicinal Products entitled *Good Clinical Practice for Trials on Medicinal Products in the European Community*.

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116. See Jones, *U.K. Applications Submitted to the CPMP*, 20 DRUG INFO. J. 373, 376 (1986). For example, since the multi-state procedure for obtaining marketing authorization in the EEC was established, at least 38 applications for marketing authorization have been objected to by at least one Member State so that all 38 applications have been referred to the CPMP. See Teijgeler, *infra* note 117.

117. Teijgeler, *The Committee for Proprietary Medicinal Products (CPMP)—Past History and Future Changes*, 20 DRUG INFO. J. 367, 368 (1986).

118. Kaufner, *The Impact of Regulation on New Product Development in the Drug Industry: A European Perspective*, in DEREGULATION OR RE-REGULATION? REGULATORY REFORM IN EUROPE AND THE UNITED STATES 171 (G. Majone ed. 1990).

119. O.J. EUR. COMM. (No. L 147) 13 (1975) [hereinafter 75/319/EEC].

120. Teijgeler, *supra* note 117, at 369.

121. 75/319/EEC, *supra* note 119, at 15.

122. See Teijgeler, *supra* note 117, at 369.

1. *Notice to Applicants.* The Notice to Applicants<sup>123</sup> was recently published to facilitate the application procedure used in the EEC for medicinal products. Its purpose is to aid regulatory authorities in establishing a consistent set of application guidelines and procedures.<sup>124</sup> The CPMP hopes that the use of a standardized set of guidelines will reduce different opinions given to the clinical data by the regulatory authorities.<sup>125</sup> The CPMP reasons that if the application procedure is consistent throughout the EEC, a regulatory agency can more easily grant a marketing authorization for a new medicinal product if another Member State has already done so from the same application.<sup>126</sup>

The Notice contains the requirements to sufficiently organize and present the data to a regulatory authority when applying for a marketing authorization.<sup>127</sup> The Notice also describes, in detail, the administrative steps to follow when applying for a marketing authorization according to the multi-state procedure.<sup>128</sup> The multi-state procedure enables a company which has previously obtained marketing authorization from one Member State to request the extension of that authorization to two or more other Member States.<sup>129</sup> The

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123. COMMISSION OF THE EUROPEAN COMMUNITIES, 2 THE RULES GOVERNING MEDICINAL PRODUCTS IN THE EUROPEAN COMMUNITY (1989) (Notice to Applicants for Marketing Authorizations for Medicinal Products for Human Use in the Member States of the European Community) [hereinafter Notice to Applicants].

124. *Id.* at 3.

125. *Id.*

126. *Id.* See generally Schnieders, *Evaluation Report of the CPMP*, 20 DRUG INFO. J. 377 (1986).

127. Notice to Applicants, *supra* note 123, at 3. The Notice to Applicants provides all the information necessary to submit an application to any one of the Member States. A brief overview of the topics covered in the manual include: preparing an application based upon the multi-state procedure (subject to Directive 83/570/EEC); preparing an application based upon the special concentration procedure for biotechnology or high technology medicinal products (subject to Directive 87/22/EEC); general information regarding basic guidelines and authorities to contact regarding the application; and two separate annexes which describe the standard format for applications in the EEC and the use of expert reports in support of an application.

In Annex I, requirements are listed as to the form and structure of the submission of the general administrative data: the chemical and pharmaceutical documentation, the pharmacological and toxicological documentation, and the clinical documentation. In Annex II, requirements are listed as to the presentation of the expert reports which must be submitted by the manufacturer as part of the application. For example, the expert must comment on the suitability of the animals used, the experimental conditions, and the reliability and applicability of the results.

128. *Id.* at 5. There are two application procedures, in addition to purely national registration procedures, which are intended to facilitate the adoption of a common position by Member States on applications for authorization of medicinal products. The first (and more widely used) procedure, governed by 83/580/EEC, is known as the multi-state procedure and enables a company which has previously obtained authorization from one Member State to request the extension of that authorization to two or more other Member States. The Member States who receive an application are obliged to take the original authorization into due consideration and should normally grant authorization within 120 days. However, if a Member State is not satisfied with the application, it may lodge its reasoned objection with the CPMP which is then required to give an opinion as to whether the product satisfies the criteria for authorization. For further details, see The Rules Governing Medicinal Products for Human Use, *supra* note 109, at 10-11.

The second and more recently established procedure, governed by 87/22/EEC, applies to medicinal products derived from biotechnology. The CPMP issues an opinion on whether the product satisfies the criteria for authorization laid down in the Community Directives. This opinion is communicated to the Member States who are required to reach a definitive decision within 30 days.

129. Notice to Applicants, *supra* note 123, at 5.

multi-state procedure assists pharmaceutical manufacturers in distributing their product throughout the EEC by requesting that additional Member States grant marketing authorization after one Member State has already done so.

Finally, the Notice provides general guidance on how the applications should be presented, the order of presentation, and the content of the dossier.<sup>130</sup> The Notice is important because it requires applicants for marketing authorizations to use the same application procedure, thereby making it more difficult for drug regulatory agencies to justify different opinions rendered on the same clinical data presented in the same format.

2. *Assessment Reports.* Besides the Notice to Applicants, the CPMP, in its effort to reduce the different opinions rendered on the same clinical data, also created assessment reports. Member States use assessment reports when considering applications based on the multi-state procedure.

Once an application for a marketing authorization has been submitted to one of the regulatory authorities of a Member State, the regulatory authority must draft an assessment report and comment on the application.<sup>131</sup> The assessment report acts as an update, summarizing the application as it was decided by the agency which received the original application.<sup>132</sup> It must be prepared the first time each agency receives an application for a new substance, irrespective of whether the decision to distribute the new substance is positive or negative.<sup>133</sup> Furthermore, it is drawn up at each phase of the approval and kept up to date after approval.<sup>134</sup> The up-dated information includes a summary of any additional data, agency assessments and conclusions of this data, the action taken by the agency, and the up to date summary of the product characteristics.<sup>135</sup> The agency is then required to forward the assessment report to other regulatory agencies where marketing authorization is sought.<sup>136</sup>

The assessment report is beneficial because it allows Member States to exchange and evaluate respective decisions regarding the approval or rejection of specific applications. In the future, the exchange of the reports should help provide for a consistent evaluation of an application.<sup>137</sup> The reports should also help in evaluating the practice of both the manufacturers and the regulatory agencies, which is necessary for reaching the goal of mutual recognition of clinical data.<sup>138</sup>

### 3. *Good Clinical Practice for Trials on Medicinal Products in the European*

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130. Poggiolini, *Drug Registration in Europe and the EEC*, 20 DRUG INFO. J. 363, 364 (1986).

131. *Id.* at 363-64.

132. Schnieders, *supra* note 126, at 380.

133. *Id.*

134. *Id.*

135. *Id.*

136. *Id.*

137. *Id.* at 382.

138. The Rules Governing Medicinal Products for Human Use, *supra* note 109, at 2.

*Community*. In November 1990, the CPMP Working Party on Efficacy of Medicinal Products published a Note for Guidance entitled *Good Clinical Practice for Trials on Medicinal Products in the European Community*.<sup>139</sup> As its name implies, the objective of this guideline is to establish the principles for the standard of good clinical practices for trials on medicinal products in human beings within the EEC. The stated purpose of the guideline is for

[a]ll parties involved in the evaluation of medicinal products [to] share the responsibility of accepting and working [subject] to such standards in mutual trust and confidence. Pre-established, systematic written procedures for the organization, conduct, data collection, documentation and verification of clinical trials are necessary to ensure that the rights and integrity of the trial subjects are thoroughly protected and to establish the credibility of data and to improve the ethical, scientific and technical quality of trials. These procedures also include good statistical design as an essential prerequisite for credibility of data and moreover, it is unethical to enlist the cooperation of human subjects in trials which are not adequately designed. [This includes] all data, information and documents [which] may be confirmed as being properly generated, recorded and reported.<sup>140</sup>

The significance of this guideline can not be over emphasized, as the standards set forth dictate how the clinical trials should be operated in order to assure acceptance of clinical data in support of a marketing authorization. Also, the guideline thoroughly discusses various aspects of clinical testing which are either not addressed at all, or insufficiently addressed, by its FDA counterpart.<sup>141</sup> For example, the glossary defines such terms as a case report form,<sup>142</sup> good clinical practice,<sup>143</sup> quality assurance,<sup>144</sup> and trial master file,<sup>145</sup> none of which are

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139. COMMISSION OF THE EUROPEAN COMMUNITIES, CPMP Working Party on Efficacy of Medicinal Products, *Good Clinical Practice for Trials on Medicinal Products in the European Community* (1990) (approved by the CPMP, Nov. 1990; effective July 1, 1991) (available from the Commission of the European Communities, Rue de la Loi 200, 8-1049, Brussels, Belgium).

140. *Id.* at 1 (Foreword).

141. For the sake of brevity, differences between FDA policy and EEC policy, based upon this new guideline, are discussed in subsequent footnotes rather than in the text. See *infra* notes 142-60 and accompanying text.

142. A case report form is defined as "a record of the data and other information on each subject in a trial as defined by the protocol. The data may be recorded on any medium, including magnetic and optical carriers, provided that there is assurance of accurate input and presentation, and allows verification." *Good Clinical Practice for Trials on Medicinal Products in the European Community*, *supra* note 139, at 6.

143. Good clinical practice is defined as "a standard by which clinical trials are designed, implemented and reported so that there is public assurance that the data are credible, and that the rights, integrity and confidentiality of subjects are protected." *Id.* at 8.

defined by FDA. Additionally, some definitions in the glossary are more demanding or more comprehensive than their FDA counterpart, such as: audit (of a trial),<sup>146</sup> clinical trial,<sup>147</sup> investigator,<sup>148</sup> and protocol.<sup>149</sup>

Besides the glossary, the guideline contains five chapters which explain the most important aspects of performing a clinical trial and which identify those areas that require closer scrutinization by the sponsor before an application for marketing authorization is sought. The first section covers the protection of trial subjects,<sup>150</sup> consultation by ethics committees,<sup>151</sup> and properly obtaining

144. Quality assurance is defined as "systems and processes established to ensure that the trial is performed and the data are generated in compliance with Good Clinical Practice including procedures for ethical conduct, SOPs, reporting, personal qualifications etc. This is validated through in-process quality control and in- and post-process auditing, both being applied to the clinical trial process as well as to the data." *Id.* at 10.

145. A trial master file is "a hard copy of all the documentation relating to a clinical trial. . . ." *Id.* at 12.

146. The glossary indicates that an audit "must be conducted either through an internal facility at the sponsor but independent of the units responsible for clinical research, or through an external contractor." *Id.* at 5 (emphasis added). The FDA, on the other hand, does not require audits.

147. The glossary defines clinical trial as "any systematic study on medicinal products in human subjects whether in patients or non-patient volunteers in order to discover or verify the effects of and/or identify any adverse reaction to investigational products, and/or to study their absorption distribution, metabolism and excretion in order to ascertain the efficacy and safety of the products." *Id.* at 6. The FDA, however, omits dosage studies from its definition of clinical trial.

148. The glossary defines an investigator as:

one or more persons responsible for the practical performance of a trial and for the integrity, health and welfare of the subjects during trial. The investigator is:

- an appropriately qualified person legally allowed to practice medicine/dentistry,
- trained and experienced in research, particularly in the clinical area of the proposed trial,
- familiar with the background to and the requirements of the study,
- known to have high ethical standards and professional integrity....

*Id.* at 9. The FDA does not require the investigator to possess an M.D. or a D.D.S.

149. Protocol is defined as "a document which states the rationale, objectives and statistical design and methodology of the trial, with the conditions under which it is to be performed and managed. A list of items to be included in the protocol is given in the Annex." *Id.* at 10. The Annex then spells out, at length, the items which should be covered in the protocol, such as: general information, justification and objectives, ethics, a general time schedule, general design, subject selection, treatment, assessment of efficacy, adverse events, practicalities, handling of records, evaluation, statistics, financing, reporting, approvals, insurance, a summary, any relevant supplements, and any references. *Id.* at 39-43. This explanation and the relevant portions of the annex make this definition of protocol much more comprehensive than that of the FDA.

150. The guideline indicates that the Declaration of Helsinki is the accepted basis for clinical trial ethics.

151. The guideline indicates that the "sponsor and/or investigator must request the opinion of relevant Ethics Committee(s) regarding suitability of clinical trial protocols . . . and of the methods and material to be used in obtaining and documenting [patient] informed consent." *Good Clinical Practice for Trials on Medicinal Products in the European Community*, *supra* note 139, at 13 (emphasis added). However, the guideline goes on to say that the "[s]ponsor/investigator should consider recommendations made by the Ethics Committee," thereby indicating that the sponsor/investigator is not compelled to follow the ethics committee recommendation(s).

Regardless of whether their recommendations are mandatory, the Ethics Committee should consider the following aspects of the proposed clinical trial which are beyond FDA requirements:

[T]he suitability of the protocol in relation to the objectives of the study, its scientific

patient informed consent.<sup>152</sup> The second section discusses the responsibilities of the sponsor,<sup>153</sup> monitor,<sup>154</sup> and investigator<sup>155</sup> during the performance of the clinical trial.<sup>156</sup> The third section explains how to handle the data derived from the clinical trial, *i.e.*, the duties of the investigator and sponsor, archiving the data, and which language to use.<sup>157</sup> The fourth section discusses how to use statistics throughout the performance of the clinical trial, particularly in experimental design, randomization and blinding, and statistical analysis.<sup>158</sup> Lastly, a system of quality assurance must be employed and implemented by the sponsor, conducted by persons or facilities *independent* of those responsible for the trial.<sup>159</sup>

Finally, at the end of the guideline is an annex which is intended to provide

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efficiency *i.e.* the potential for reaching sound conclusions with the smallest possible exposure of subjects, the justification of predictable risks and inconveniences—weighed against the anticipated benefits for the subjects and others. . . .

[P]rovision for compensation/treatment in the case of injury or death of a subject if attributable to a clinical trial, and any insurance or indemnity to cover the liability of the investigator and sponsor. . . .

152. The guideline indicates that the Declaration of Helsinki should be implemented in each clinical trial concerning the principles of informed consent. However, the guideline appears to permit oral consent where an independent witness can record the patient's consent. *Id.* at 16. The FDA, however, does not permit such oral consent. Additionally, the guideline indicates that "[c]onsent must always be given by the signature of the subject in a non-therapeutic study, *i.e.*, when there is no direct clinical benefit to the subject." *Id.* The FDA has no such distinction.

153. The guideline indicates numerous duties which go beyond FDA requirements for which the sponsor is accountable. For example, the sponsor must establish detailed standard operating procedures to comply with good clinical practices; must conduct an internal audit of the trial; must submit notification/application to the relevant regulatory authorities; must ensure submission of any necessary documents to the Ethics Committee; must ensure communication of any modification, amendment or violation of the protocol (if the change may impact on the subject's safety); must inform the investigator and relevant authorities about discontinuation of the trial and the reasons therefore; must retain sufficient samples of each batch and a record of its analyses and characteristics for reference so that there is the possibility for an independent laboratory to re-check the investigational products; and the sponsor must provide adequate compensation or treatment for subjects in the event of trial related injury or death, and provide indemnity (legal and financial) for the investigator, except for claims resulting from malpractice and/or negligence (*cf.* FDA regulations which only require a statement in the patient consent form on whether compensation is available). *Id.* at 17-19.

154. The guideline indicates that a "monitor" is the principal communication link between the sponsor and the investigator and, as such, has numerous responsibilities. *Id.* at 20. The FDA has no similar requirement.

155. The investigator is responsible for a number of duties which go beyond FDA regulations. For example, the guideline indicates that the investigator is responsible for making all data available to the sponsor/monitor and any other relevant authority for verification, audit, or inspection purposes, whereas there is no sponsor access to medical records in FDA regulations (the FDA recommends that it be in the patient consent form). Also, the guideline indicates other areas for which the investigator is responsible, *e.g.*, providing fully functional resuscitation equipment in case of emergency, etc., whereas the FDA regulations do not specifically include these additional requirements.

156. *Good Clinical Practice for Trials on Medicinal Products in the European Community*, *supra* note 139, at 17-24.

157. *Id.* at 25-28.

158. *Id.* at 29-30.

159. *Id.* at 31.



guidance on some of the practical aspects of clinical trials.<sup>160</sup> For example, it briefly defines the four phases of clinical trials related to the development of medicinal products; it indicates measures to ensure optimal trial conditions; it describes what the trial protocol must consist of; it describes the purpose of the case report form; it indicates what information must be disclosed regarding the financing of the trial; and it also discusses insurance and liability aspects, labelling, and systems of notification or approval of clinical trials.

The careful analysis and preparation contained in the guideline indicates that the CPMP is committed to obtaining a consistent recognition of clinical data in the EEC. Hopefully, the guideline, along with the Notice to Applicants and the assessment reports, will assist pharmaceutical manufacturers in obtaining marketing authorization earlier than before.

4. *Future Trends.* The recent developments of the Notice to Applicants, assessment reports, and the guideline on good clinical practice are encouraging because they increase communication between drug regulatory agencies which can foster the increased acceptability of foreign clinical data. For example, the Notice to Applicants procedure is increasingly being used by other Western European countries which are not members of the European Community.<sup>161</sup>

In addition to increasing communication between regulatory agencies, these three methods can also reduce the different opinions reached on the same clinical data by the Member States. This can be explained by briefly examining the CPMP appeals process.

The CPMP employs an appeals process to reduce the different opinions on the same clinical data.<sup>162</sup> When a pharmaceutical manufacturer has received a marketing authorization from one Member State, the multi-state procedure is usually employed so that marketing authorizations can be acquired from two or more other Member States.<sup>163</sup> On the basis of the application and the authorization granted by the first Member State, the authorities of the Member States to which the application is addressed have 120 days to grant authorization to market the product in their country, or to formulate reasoned objections.<sup>164</sup> Where one or more objections are advanced, the matter is referred to the CPMP which considers the grounds for the objections, and any written or oral explanations provided by the applicant, before issuing its own reasoned opinion within sixty days.<sup>165</sup>

This appeals process should help the CPMP in reducing the different opinions on the same clinical data because the individual regulatory agencies must now

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160. *Id.* at 35-46.

161. Notice to Applicants, *supra* note 123, at 2.

162. It should be noted that the CPMP can only make suggestions as to the acceptance or rejection of a certain application; the decision is not binding on the Member State. See Notice to Applicants, *supra* note 123, at 3.

163. See *supra* notes 128-129 and accompanying text.

164. Notice to Applicants, *supra* note 123, at 5.

165. *Id.*

follow the Notice to Applicants, assessment reports, and good clinical practice procedures. These procedures help the CPMP reduce the different opinions because they decrease the possibility of a regulatory agency basing their rejection of a particular application on an invalid reason, such as the source of the clinical data. The CPMP, by acting as a watchdog over the individual regulatory agencies, can ensure that these procedures are being properly followed and that the agencies are basing their decision to approve or reject an application on the proper factors. Consequently, the threat of appeal to the CPMP should deter regulatory agencies from basing a rejection of a marketing authorization on such a factor as the source of the foreign clinical data.

The Notice to Applicants, assessment reports, and the guideline to good clinical practice should be required on an international scale so that an exchange of information can occur between more countries, and not just between those located in Europe. For example, the FDA could benefit from the use of assessment reports in determining the basis for another agency's decision to approve or reject a particular new drug. In the long run, what may come out of such guidelines is a common application format, along with common guidelines for good clinical practice, not only for the EEC countries, but also the U.S. and perhaps the rest of the international community.<sup>166</sup>

#### IV. REDUCING THE BARRIERS WHICH INHIBIT THE INTERNATIONAL ACCEPTANCE OF FOREIGN CLINICAL DATA

##### A. *Understanding the Barriers*

The decisive factor in assessing an application for marketing authorization should be the *quality* of the clinical data, irrespective of origin.<sup>167</sup> The reasons for concentrating on the quality of the clinical data, as opposed to concentrating on its origin, are both legal and scientific.<sup>168</sup> First, as explained above, both FDA and EEC laws require it.<sup>169</sup> Second, from the scientific standpoint, data generated in one country is nearly always applicable in other countries; the exceptions lie only where ethnic factors may prohibit extrapolation or where medical terminology varies.<sup>170</sup>

Unfortunately, however, quality is not always the only factor considered by a drug regulatory agency when reviewing an application. Two different but related factors that inhibit the acceptability of foreign clinical data are: 1) national barriers, and 2) economic and political forces.

##### 1. *National Barriers.* "[N]ational barriers should not inhibit the international

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166. See Teiggeler, *supra* note 117, at 370.

167. Knabe, *Acceptance of Foreign Clinical Data in Industry*, 22 DRUG INFO. J. 137, 139 (1988).

168. Jones, *supra* note 70, at 95.

169. See *supra* notes 27-44, 108-15 and accompanying text.

170. Jones, *supra* note 70, at 95.

movement of a new and more effective drug product. The consumer is entitled to as much product effectiveness as the industry can safely deliver in the particular drug, once safety is reasonably shown.<sup>171</sup>

National barriers act as a type of prejudice against another country's standards for granting a marketing authorization. For example, if a regulatory agency in the EEC grants a marketing authorization for a new medicinal product, then distribution of that product can only occur within the boundaries of that Member State. If the sponsor of the marketing authorization seeks to distribute the product to other Member States, the multi-state procedure is used and the second Member State receives the application and reviews the original marketing authorization granted by the first Member State.<sup>172</sup> The second Member State can then reject the marketing authorization based upon its opinion that the quality of the data is deficient, and it can discredit the original Member State's approval if it believes the procedures employed by the original Member State were inadequate.

Although the procedures employed by the original Member State are certainly a legitimate concern for the subsequent Member State reviewing the application, often this is only used as an excuse to reject a particular application. Thus, even though national barriers are not to be taken into account, regulatory agencies are often influenced by the historical background of the Member State in question<sup>173</sup> rather than on the quality of the data supplied. Since the goal of every pharmaceutical company or drug regulatory agency must be to increase the safety and usefulness of drugs reaching the marketplace, "we should question whether a national border is an appropriate dividing line"<sup>174</sup> for the acceptability of foreign clinical data.

2. *Economic and Political Forces.* "[D]ifferent cultures can make very different value judgments about important life-sustaining drugs. . . . [E]ach nation makes its own judgment of what levels of harm can be tolerated by its people."<sup>175</sup>

Economic and political forces can be explained in terms of a risk balancing which involves a number of nonmedical or nonsafety judgments for the people guarding the gate of drug product entry into a nation.<sup>176</sup> Agency officials often engage in trade-offs between economic and political forces which can compete with the decision to grant or deny a particular application. For example, in a particular country there may be a higher cost for the drug, there may be a disadvantage to an indigenous industry, or there may be a higher potential for adverse reactions which may alter an agency's decision to grant approval for a

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171. O'Reilly, *supra* note 11, at 133.

172. See *supra* notes 128-129 and accompanying text.

173. Teiggeler, *supra* note 117, at 368.

174. O'Reilly, *supra* note 11, at 132.

175. *Id.* at 136.

176. *Id.* at 133.

particular new drug.<sup>177</sup> Additionally, in the EEC, a "marketing authorization" by a national drug regulatory agency is no permission to actually market the product. In most Member States a new drug has to pass through a lengthy evaluation process to determine its economic benefits and costs for the purpose of fixing its price and reimbursement rate.<sup>178</sup>

Political accountability is also involved. If an agency official is expected to be accountable for a particular regulatory decision regarding a new drug application, a decision to grant approval may change. For example, "[t]he 'Weiss effect'<sup>179</sup> or the 'Waxman scenario'<sup>180</sup> are critiques of FDA staff performance which directly impact on future discretionary decisions of FDA employees. The French or German civil services presumably face their own equivalents of political accountability for drug decisions."<sup>181</sup>

Because of external forces such as national barriers and economic and political forces, drug regulatory agencies do not rely solely on the quality of the data supplied by the sponsor in the new drug application. Accordingly, these barriers must be reduced in order to increase the acceptability of foreign clinical data, which will result in improved health care by increasing the availability of new drugs.

### B. Reducing the Barriers

Regulatory agencies should take a threefold approach to reduce the barriers which block the acceptance of foreign clinical data: increase methods of communication between agencies through the use of MOUs, CROs, and assessment reports; reduce economic and political pressures; and establish an international drug dossier.

1. *Increasing Methods of Communication.* As discussed above, the FDA has employed Memorandums of Understanding with various national health authorities.<sup>182</sup> This method of opening up channels of communication may be the best method to increase the acceptance of foreign *clinical* data because the regulatory agencies themselves instigate these agreements. By voluntarily opening channels of communication between themselves, regulatory agencies observe what procedures are being used in other countries. Since MOUs also

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177. *Id.*

178. Kaufer, *supra* note 118, at 172. See also O'Reilly, *supra* note 11, at 137.

179. The "effect" comes from the relentless questioning of FDA decisions during hearings conducted by Rep. Ted Weiss, *Hearings, The Regulations by the Department of Health and Human Services of Carcinogenic Color Additives, Before a Subcomm. of the House Comm. on Government Operations*, 98th Cong., 2d Sess. 511 (1984). O'Reilly, *supra* note 11, at 136 n.19.

180. Chairman Waxman's efforts to change new drug approval processes led ultimately to the 1984 legislation, Pub. L. No. 97-417, 98 Stat. 1585 (1984), and he pressed FDA to make changes. *Hearings, Drug Legislation, Before a Subcomm. of the House Comm. on Energy and Commerce*, 98th Cong., 1st Sess. (1983). O'Reilly, *supra* note 11, at 136 n.20.

181. O'Reilly, *supra* note 11, at 136.

182. See *supra* notes 94-96 and accompanying text.

involve the joint use of inspectors and the exchange of inspection report results,<sup>183</sup> regulatory agencies are constantly involved in communication with other agencies. As a result, the agencies will eventually grow familiar with one another, which can result in the acceptance of clinical data, and not just pre-clinical data.<sup>184</sup> Once such familiarity is established between regulatory agencies, personnel from the respective agencies and also private industry can anticipate what procedures must be employed to achieve an acceptable standard for the foreign clinical data.

CROs can also facilitate the acceptance of foreign clinical data because, once properly qualified by a regulatory agency, the agency may be more willing to accept a future study from that particular CRO. The more often a particular CRO is used, the more often a regulatory agency is likely to accept the foreign clinical data because the agency has become familiar with the CRO through experience.

Unfortunately, using MOUs and CROs to achieve the goal of mutual recognition appears utopian in nature because this requires regulatory agencies to expend a great deal of time, effort and money. One solution to this involves requiring assessment reports on an international scale. Assessment reports should be required on an international scale because this would provide every drug regulatory agency in the world with an updated history of the new drug product. This way, drug regulatory agencies will stay apprised of new drugs being approved by other agencies, with the hope that deference will be granted to an agency which has already granted marketing authorization to a sponsor for a new drug product. Also, since the CPMP has already undertaken such a procedure, the application of assessment reports internationally would not be extremely costly or time consuming; regulatory agencies would merely have to require the use of such reports internationally and make available to sponsors the appropriate information and forms. If mutual recognition of foreign clinical data is to occur, assessment reports must be required on an international scale to increase the methods of communication between nations.

2. *Reducing Economic and Political Forces.* As discussed above, acceptability of a foreign study by FDA, CPMP, and other authorities has often been conditioned upon external forces rather than on the quality of the data itself.<sup>185</sup> Consequently, the harmonization of national laws alone will not result in the same attitude on the part of drug regulatory agencies to accept or deny a particular application, nor will the same results be achieved.<sup>186</sup> Thus, economic and political factors must also be reduced so that a consistent evaluation of applications can occur.

In order to minimize economic effects upon a sponsor seeking approval for a

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183. See Buday, *supra* note 94 and accompanying text.

184. See generally Buday, *supra* note 94, at 49; Halperin, *supra* note 19, at 153.

185. See *supra* notes 167-81 and accompanying text.

186. Teijgeler, *supra* note 117, at 368.

new drug, the best advice is to obtain information about the foreign regulatory agency before the approval process begins. For example, consultants can be retained to recommend what local customs exist in processing the product approval or other clearance.<sup>187</sup> The firm requesting foreign approval should also allocate additional time in seeking approval, especially for the unforeseen procedural pitfalls, such as translation.<sup>188</sup>

Although it is unrealistic to think that economic pressures will fully dissolve, the pharmaceutical manufacturer can prepare for such encounters by being aware that they exist and by taking appropriate steps to reduce the obstacles. Furthermore, if private industry reminds agency officials that external factors such as economic and political forces should not be relied upon in determining the outcome of a particular marketing application, then perhaps the agency will concern itself more with the scientific and medical impact a new drug provides, rather than on hypothetical political effects.

3. *Establishing an International Drug Dossier.* An international registration dossier is a comprehensive scientific document used to obtain worldwide licensing approval of a drug by diverse health authorities.<sup>189</sup> Its purpose is to condense the various regulatory requirements concerning chemical regulation into a standardized set of objective criteria in order to establish a uniform acceptance of research data.<sup>190</sup> A comprehensive, cohesive, well-referenced and professionally written dossier can assure expeditious handling by registration authorities and, more likely than not, an early approval of the license application.<sup>191</sup>

The international dossier concept has been discussed by experts in drug development, and the EEC has move partly toward that goal. Its equivalent in the field of chemical regulation has been vigorously debated by chemical experts who are trying to make the U.S. chemical approval system more like that of the EEC system. Some form of "passport" for U.S. chemical developments may be seen within ten years. In the drug field, we are very likely to see evolution of a *de facto*, if not a *de jure*, uniformity of acceptance for research data, controls and chemistry sections, bio-equivalence testing methods, and manufacturing quality controls.<sup>192</sup>

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187. O'Reilly, *supra* note 11, at 137.

188. *Id.*

189. Buday, *The Mechanics of Assembling an International Drug Dossier*, 17 DRUG INFO. J. 133 (1983). The factors to take into consideration of assembling such a dossier are planning and scheduling of the dossier; creating, organizing and formatting; typing; copying and collating; working with extramural suppliers and services; and shipping the document to the field. *Id.*

190. O'Reilly, *supra* note 11, at 134.

191. Buday, *supra* note 189, at 138.

192. O'Reilly, *supra* note 11, at 134.

However, even though the concept of an international drug dossier has received some attention in recent years,<sup>193</sup> implementing the dossier concept has not achieved any considerable international success. A company wishing to establish such a dossier must undertake an enormous amount of time and money to research the necessary requirements before beginning such a dossier.<sup>194</sup> However, since the CPMP has employed the Notice to Applicants procedure,<sup>195</sup> implementation of an international dossier system can be based on the European system by expanding the procedure to international proportions. If the CPMP system can be applied to achieve a dossier which is appropriate and satisfactory for all concerned, then the international dossier plan can succeed.

In summary, increasing the methods of communication by using more MOUs, CROs, and assessment reports, by reducing economic and political forces, and by establishing an international drug dossier, the obstacles associated with the international acceptance of foreign clinical data can be reduced. For this to work, however, regulatory agencies need to first recognize that concerted action must be taken on an international scale. Ultimately, more international meetings between these regulatory agencies are needed with the topic of foreign clinical data on the agenda. Also, these channels of communication, once opened, must remain continually open if the increased acceptability of foreign clinical data is to make any impact at all upon the increased availability of pharmaceutical drugs.

#### CONCLUSION

As stated in the Introduction, Beth and Bill are just two examples of patients who do not have access to helpful drugs which are available in other countries. Because there are thousands of patients like Beth and Bill, drug regulatory agencies must reduce the barriers which inhibit the free flow of pharmaceutical drugs internationally. The drug lag is just one of the unfortunate effects that results from agencies who reject foreign clinical data. And, if the drug lag continues, so will our health care problems because patients will be unable to obtain innovative new drugs.

The problems associated with the international acceptance of foreign clinical data have become readily apparent to national drug regulatory agencies, particularly the FDA and CPMP. As a result of this awareness, these agencies have adopted standards in determining when foreign clinical data will be acceptable. However, these agencies face problems applying a consistent interpretation to these standards. This prevents international pharmaceutical manufacturers from anticipating what studies will be acceptable. To achieve a consistent interpretation of an application, national barriers and economic and political forces must be reduced.

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193. See O'Reilly, *supra* note 11, at 134; Buday, *supra* note 189, at 133.

194. See generally Buday, *supra* note 189, at 133.

195. See *supra* notes 123-30 and accompanying text.

These barriers can be reduced by increasing methods of communication through the use of MOUs, CROs, and by requiring assessment reports to be used on an international scale. Also, establishing an international drug dossier system can hasten the approval process if the European Notice to Applicants procedure is implemented on an international scale. If such steps can be made in the near future, patients like Beth and Bill may be able to obtain the drugs which could save their lives.

*John J. Gorski\**

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