The U S Export of "Pipeline" Therapeutic Drugs

Rebecca J. Cook*

INTRODUCTION

In the past decade there has been extensive debate about the export of therapeutic drugs and devices[1] that are not yet approved for use in the United States (U.S.), but are in the pipeline for approval. This debate has been part of larger controversy sur rounding the export of a number of potentially hazardous products, such as pesticides.[2] It also reflects the impatience other countries experience due to the delay in approval which results from the U.S. process of drug screening. The U.S. drug screening process emphasizes pre-marketing determination of safety and effectiveness by a long duration of testing. An alternative process used, for instance, in the United Kingdom, permits ear lier marketing through less extensive pre-market testing but re quires more post-market monitoring than does the U.S. process, and has a higher rate of recall of initially approved products.[3]

This article examines U.S. regulatory actions, under the Federal Food Drug and Cosmetic Act (FDC Act),[4] that determine the acceptability of medical drugs and devices. It outlines the newly enacted Drug Export Amendments Act of 1986 (the 1986 Act),[5]

Assistant Professor of Clinical Public Health and Staff Attorney, Development Law and Policy Program, Center for Population and Family Health, Columbia University School of Public Health. J.S.D. Candidate, Columbia University School of Law.

1. *See generally* Duby, *Sovereignty v. Paternalism: The Export of Nonconforming Drugs and Devices*, 37 FOOD DRUG COSM. L.J. 409 (1982).

2. *See generally* Alston, *International Regulation of Toxic Chemicals*, 7 ECOLOGY L.Q. 397 (1978); Interagency Working Group on Hazardous Substances Export Policy: Draft Report, 45 Fed. Reg. 53,754 (1980).

3. *See generally* Teff, *Drug Approval in England and the United States*, 33 AM. J. COMP LAW 567 (1985).

4. Federal Food, Drug, & Cosmetic Act of 1938, as amended, 21 U.S.C. §§ 301-392 (1982). *See also* CONTROLLING THE USE OF THERAPEUTIC DRUGS: AN INTERNATIONAL COMPARISON (W.M. Wardell ed. 1978) (comparison with other national regulatory laws and policies).

5. Drug Export Amendments Act of 1986, Pub. L. No. 99-660, 1987 U.S. CODE CONG. & AD. NEWS (100 Stat.) *adding* § 802 ("Exports of Certain Unapproved Products") to Subch. VIII ("Imports and Exports") of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 381 (1982) [hereinafter Drug Export Amendments Act of 1986]. The United States is

which enables the U.S. export of certain drugs that are in the pipeline for approval.[6] Pipeline drugs are defined as those drugs that are exempted from prohibition of distribution in order to permit clinical investigation;[7] and for which the sponsor is actively pursuing approval but has not yet filed a new drug application (NDA) for the approval of distribution.[8] The export provisions of the 1976 Device Amendments enabling the export of certain devices[9] are also described.

It also discusses how the regulatory approach attempts to balance U.S. responsibility to respect the rights of foreign nations to make their own decisions regarding their imports and to ensure the export of safe and effective products. Lastly this article outlines the opposing views on export policy and some of the legislative proposals that preceded and, in part, led to the 1986 Act, and assesses the guidelines established by the 1986 Act for the export of pipeline drugs.

OVERVIEW OF DRUG AND DEVICE EXPORT LAW

The policies regarding the export of therapeutic drugs and the export of medical devices that are being screened for domestic

the only major drug producing country that has prohibited the export of pipeline drugs to requesting countries. *Hearings on Exports of Unapproved Drugs, Before the Subcomm. on Health and the Environment of the House Comm. on Energy and Commerce*, 98th Cong., 2d Sess. 173-81 (1984) (statement of John Dunne, M.D., Chief of the Pharmaceuticals Unit, World Health Organization).

6. Drug Export Amendments Act of 1986, *supra* note 5, at § 802(b)(1)-(2). The 1986 Act enables the export of certain other unapproved products that are in the pipeline outlined in the Drug Export Amendments Act of 1986, *supra*, at § 802(a):

> A drug (including biological product) intended for human or animal use (1) which (A) requires approval by the Secretary under section 505 or section 512, or (B) requires licensing by the Secretary under section 351 of the Public Health Service Act or by the Secretary of Agriculture under the Act of March 4, 1913 (known as the Virus Serum Toxin Act), before it may be introduced or delivered for introduction into interstate commerce to country and (2) which does not have such approval or license, which is not exempt from such sections or Act, and which is introduced or delivered for introduction into interstate commerce to country, is adulterated, misbranded, and in violation of such sections or Act unless the export of the drug is authorized under subsection (b).

7 21 U.S.C. § 355(i) (1982).

8. 21 U.S.C. § 355(b), (c) (1982). Drugs that do not have an exemption for investigation, *id.*, drugs for which approval is not being sought and drugs that have not been disapproved after submission for an approval, 21 U.S.C. § 355(d) (1982), or whose approval has been withdrawn, 21 U.S.C. § 355(e) (1982), are not pipeline drugs for purposes of the 1986 Act.

9. 21 U.S.C. § 381(d)(1)-(2) (1982).

use are becoming more uniform. The FDC Act, as amended by the 1986 Act, permits the export of pipeline drugs under certain conditions.[10] Formerly the FDC Act prohibited the export of most drugs that had not yet been approved for domestic use.[11] However the FDC Act permitted, and continues to permit, the export of new drugs that had been approved for investigational use only in this country provided that the export is accompanied by certification that such drugs may be used abroad only for investigational purposes.[12] Under the 1976 Device Amendments to the FDC Act, the export of pipeline medical devices has been possible under similar conditions.[13]

Drugs

The term "drugs" refers to products developed before 1938 that were regulated by the 1906 Pure Food and Drug Act[14] before it was absorbed into the original FDC Act of 1938.[15] Drugs remain distinct from and do not fall within the definition of "new drugs" in the present law [16] Under the FDC Act, "new drugs" in principle, are drugs whose human use was developed after 1938. A drug may be considered "new" for many reasons, for example:

1. it contains a chemical not developed for human use before 1938,
2. it contains a chemical or substance not approved for use in medicine prior to 1938,
3. it contains a chemical or substance that was previously approved for use in medicine, but which is now recommended for use in different dosages or for different conditions than before,
4. it has become recognized by qualified experts as safe and effective for its intended uses as a result of investiga-

10. Drug Export Amendments Act of 1986, *supra* note 5, at § 802(b)(1)-(2).

11. 21 U.S.C. §§ 355, 381(d) (1982); U.S. v. An Article Drug Ethionamide-INH, No. 67-C-288, slip op. (E.D.N.Y. 1967), *quoted in* FOOD AND DRUG LAW INSTITUTE, FEDERAL FOOD, DRUG AND COSMETIC ACT, 1965-1968 16 (Kaplan & Kleinfeld, eds. 1973).

12. 21 U.S.C. § 355(i) (1982).

13. 21 U.S.C. § 381(d)(1)-(2) (1982).

14. Pub. L. No. 59-384, 34 Stat. 768 (1906), *repealed by* the Federal Food, Drug & Cosmetic Act, Pub. L. No. 75-717 (1938). Drugs regulated before 1938 and regulated by the 1906 Pure Food and Drugs Act were grandfathered when the 1938 Act replaced the 1906 Act. 21 U.S.C. § 321(p)(1) (1982).

15. Federal Food, Drug & Cosmetic Act of 1938, as amended, 21 U.S.C. §§ 301-392 (1982).

16. 21 U.S.C. § 321(p) (1982).

> tional studies, but has not otherwise been used to a material extent or for a material period of time.[17]

A "new drug" may not be commercially marketed in the U.S. unless it has been approved as safe and effective by the Food and Drug Administration (FDA) under the FDC Act.[18] Such approval may be given only following submission of a New Drug Application (NDA) by the sponsor of the drug.[19] The NDA must contain acceptable scientific data, including tests showing the drug s safety and substantial evidence of its effectiveness for the conditions for which it is to be labeled and offered.

The law defines "substantial evidence" as

> evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could be fairly and responsibly concluded by such experts that the drug will have the effect it purports to or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof.[20]

Before approval of an NDA, the FDA may permit a specific sponsor to use a new drug for investigational use only [21] Investigational drugs are new and as yet unapproved, drugs for which exemption from prohibition has been arranged by the FDA solely to allow investigational use by experts qualified by scientific training and experience to study the safety and effectiveness of such drugs.[22] Investigational drugs can be distributed in the United States, and can be exported or imported, but in all cases only for investigational use. Such distribution can take place only after an acceptable "Notice of Claimed Exemption for a New Drug" (IND) has been filed with the FDA by the sponsor [23] In order to suc cessfully file for an IND the sponsor has to meet the require ments governing submission of information on the planned research protocol, and must specify the details of the drug pro-

17 *Id.*, *see generally* Nightingale, *Evolving Drug Approval Process*, 40 FOOD DRUG COSM. L.J. 499 (1985).

18. 21 U.S.C. § 355(a) (1982).

19. 21 U.S.C. § 355(b) (1982).

20. 21 U.S.C. § 355(d)(5) (1982).

21. 21 U.S.C. § 355(i) (1982).

22. *Id.*

23. *Id.*

posed to be tested and the qualifications of the clinical investigators.[24]

Export to "Listed" Countries

The Drug Export Amendment Act of 1986 permits the export of a pipeline new drug for regular use if all of the following conditions are met:[25]

1. The new drug is an investigational drug (and therefore subject to an IND) for which an NDA is being actively pursued by the person who has the exemption;
2. it is being exported to a "listed" country[26] in which the drug is approved for regular use and has not been withdrawn from sale;
3. its application for approval has not been disapproved;[27]
4. the drug is manufactured, processed, packaged, and held in conformity with current good manufacturing practices and is not adulterated;[28]
5. its shipping package is labeled to show that it is authorized in the countries for which approval has been given;
6. it is not subject to a notice by the Secretary of Health and Human Services of a determination that the manufacture of the drug in the U.S. is contrary to the public health and safety

It must also meet the requirements that the drug:[29]

24. 21 U.S.C. § 355(i)(1) (1982).

25. Drug Export Amendments Act of 1986, *supra* note 5, at § 802(b)(1)(A)-(G).

26. *Id.* § 802(b)(4)(A). The 1986 Act lists the following twenty-one countries as those to which drug export is permitted, provided that each country proposed for export has approved the drug and the drug has been withdrawn from sale in that country: Australia, Austria, Belgium, Canada, Denmark, Federal Republic of Germany, Finland, France, Iceland, Ireland, Italy, Japan, Luxembourg, The Netherlands, New Zealand, Norway, Portugal, Spain, Sweden, Switzerland and the United Kingdom. Countries may be added to or deleted from the list by Congress. They may be added provided that they meet the statutory or regulatory requirements that:

1. subject drug applications to scrutiny to determine their safety and effectiveness;
2. ensure that drugs are manufactured in compliance with good manufacturing practices;
3. monitor adverse drug reactions and contain mechanisms for withdrawal of approval; and
4. ensure that labeling and promotion of drugs are done in accordance with approved regulations.

27 21 U.S.C. § 355(d) (1982).

28. The drug is deemed adulterated according to 21 U.S.C. §§ 351(a)(1), (a)(2)(A), (a)(3), (c), (d) (1982).

29. 21 U.S.C. § 381(d)(1) (1982).

1. is in accordace with the specifications of its foreign purchaser
2. complies with the laws of the importing country
3. is labeled on the outside shipping package as intended only for export, and
4. is not sold or offered for sale in U.S. domestic commerce.

In some instances, a sponsor of a new drug may be tempted to submit an NDA solely in order to gain export markets under the pipeline approval mechanism and therefore does not pursue U.S. domestic marketing approval in good faith.[30] The Secretary of Health and Human Services (Secretary) must therefore determine whether the applicant for permission to export the pipeline drug is actively pursuing an NDA by "that degree of attention and continuous directed effort as may reasonably be expected from, and are ordinarily exercised by a person before approval or licensing of a drug."[31]

The U.S. feels little obligation to protect foreign populations against U.S. pipeline drugs when their own governments maintain adequately sophisticated controls for approval of the import of drugs for therapeutic use. However when a foreign country lacks controls the U.S. considers adequate, the Secretary shall not permit the export of pipeline drugs to this country Accordingly Congress has listed in the 1986 Act those countries considered to adequately control their own drug imports.[32] Listed countries are therefore not afforded the protection of U.S. domestic standards, and the Secretary may authorize export of a pipeline drug to a listed country whose own drug regulatory authority has approved it for use within that country [33]

The Secretary may also permit the export of a pipeline drug to a listed country where it is not approved for use, and to a non-listed country provided that it is exported to such a country solely for the purposes of trans-shipment to a listed country where it is approved.[34]

The sponsor must file an application at least ninety days before the date when the applicant proposes to export the drug for

30. A good faith effort to gain U.S. approval is not required of all new drugs. *See infra* text p. 49-51 on drugs for the prevention and treatment of tropical diseases.

31. Drug Export Amendments Act of 1986, *supra* note 5, at § 802(b)(1).

32. *Id.* § 802(b)(4)(A).

33. *Id.* § 802(b)(1)(B).

34. *Id.* § 802(b)(2).

which the application is submitted.[35] The Secretary is required to publish a notice in the Federal Register before the expiration of ten days from the date of submission. This notice must identify the applicant, the drug proposed to be exported and the country to which the drug is proposed to be exported.[36]

The applicant for export must:[37]

1. identify the drug,
2. list each country to which the drug is exported and the persons to which it is to be exported, and
3. certify that the drug:
   a. will be exported only to one or more of the twenty-one listed countries in which it is approved for domestic use, unless it is already authorized for transshipment through that country[38] and will be exported only in quantities which may reasonably be sold in that importing country
   b. has not been withdrawn from sale in any listed country to which it will be exported,
   c. meets U.S. good manufacturing practices,[39]
   d. will be labeled for export to a specified country and will not be sold or offered for sale in U.S. domestic commerce,[40]
   e. has not been disapproved in the U.S.[41] and accords with the specifications of the foreign purchaser and the laws of the country intended for import,[42]
4. include certificates by the "holder"[43] that the holder "will actively pursue the approval or licensing of the drug,"
5. identify the IND for the drug for which approval of an NDA is being sought,
6. identify the establishment in which the drug is manufac tured, and

35. *Id.* § 802(b)(3)(A).

36. *Id.*

37 Drug Export Amendments Act of 1986, *supra* note 5, at § 802(b)(3)(B).

38. *Id.* § 802(b)(2).

39. In addition, it must meet all the requirements of 21 U.S.C § 381(d)(1) (1982).

40. Drug Export Amendments Act of 1986, *supra* note 5, at § 802(b)(1)(E).

41. It must meet the requirements of the Drug Export Amendments Act of 1986, *supra* note 5, at § 802(b)(1)(C).

42. It must meet the requirements of the Drug Export Amendments Act of 1986, *supra* note 5, at § 802(b)(1)(G).

43. Under the Drug Export Amendments, "holder is defined as "the holder of an application and shall be considered reference to any person who is under common control with holder, is controlled by the holder, controls the holder, is owned by the holder, or owns the holder. Drug Export Amendments Act of 1986, *supra* note 5, at § 802(g)(2).

7 include a written agreement from each importer of the drug that he will:
   a. not export the drug to a country which is not among the twenty-one listed countries,
   b. notify the exporter of any knowledge of export to an unlisted country and
   c. maintain records of the wholesale distributors to which the drug is sold.

The Secretary shall review the export application within thirty days after its submission to determine whether it meets the requirements of 1, 2, 4, 5, 6 and 7 above and contains the certification required for 3 (except the certification that the drug is approved in the country of import and that it has not been withdrawn from sale). If the application meets these requirements and contains the appropriate certifications, the Secretary shall conditionally approve the application.[44] An application which is conditionally approved will be finally approved within five days of the submission of the certification that it is approved in the country or countries of import included among the twenty-one listed countries.[45]

If the Secretary decides to disapprove an application, then he must provide a written explanation of the deficiencies that should be corrected in order for the application to be approved.[46] The applicant then has sixty days from receipt of the explanation to correct the deficiencies in the application.[47]

An application that has been approved can be amended to include additional listed countries to which the applicant wants to export which were not included in the original application.[48] The holder will submit an amendment no later than thirty days before the date of the proposed export identifying the country to which the holder intends to export and containing information sufficient to show that the drug has been approved and has not been withdrawn from sale in that country [49] The Secretary will approve or disapprove the amendment within fifteen days of receipt of the notice of amendment.[50]

44. Drug Export Amendments Act of 1986, *supra* note 5, at § 802(b)(3)(C)(i).
45. *Id.*
46. *Id.* § 802(b)(3)(C)(ii).
47 *Id.* § 802(b)(3)(C)(ii)(II).
48. *Id.* § 802(b)(3)(D).
49. *Id.*
50. *Id.*

The holder of an approved application for export shall report to the Secretary:

1. any withdrawal of approval of the drug by any country to which it has been exported or approved for export,
2. any withdrawal from sale in any such country
3. the withdrawal of an application for an NDA, and
4. the receipt of any "credible" information indicating that the drug is being or may have been exported from one of the listed countries to an unlisted country within fifteen days of the holder's receipt of information of the event.[51]

The holder of an approved application for export of a drug is required to report annually to the Secretary on actions taken to secure the marketing approval of the drug in the U.S. during the previous year.[52] The Secretary shall determine whether the holder is actively pursuing approval no later than ninety days from the date of the report.[53] If the Secretary determines that the approval is not being actively pursued, the holder has sixty days from receipt of notice of such determination to assure the Secretary that necessary actions are being taken for approval.[54] During the sixty day period, the Secretary shall give the holder an opportunity for an informal hearing on the determination.[55] If upon expiration of the sixty day period, the Secretary believes that approval of such drug is not being actively sought, the Secretary shall prohibit the export of such a drug.[56]

A drug authorized to be exported to a country under an approved application[57] may not be exported if[58] approval or sale of the drug is withdrawn by the listed importing country an NDA filed for approval in the U.S. is refused[59] or an investigational drug exemption is withdrawn.[60]

The Secretary may prohibit export by a determination[61] that a drug for which an application was approved no longer complies

51. Drug Export Amendments Act of 1986, *supra* note 5, at § 802(c)(1).
52. *Id.* § 802(c)(2).
53. *Id.*
54. Drug Export Amendments Act of 1986, *supra* note 5, at § 802(e)(2).
55. *Id.*
56. *Id.*
57 Drug Export Amendments Act of 1986, *supra* note 5, at § 802(b).
58. *Id.* § 802 (d).
59. 21 U.S.C. § 505 (1982).
60. 21 U.S.C. § 355(i) (1982).
61. Drug Export Amendments Act of 1986, *supra* note 5, at § 802(e)(1).

with certain conditions of being a pipeline drug;[62] does not meet the requirements of either good manufacturing practices or non-adulteration;[63] does not comply with shipping requirements;[64] does not meet the requirements of the foreign country;[65] or that the manufacture for export is contrary to the public health and safety of the U.S.[66] After such a determination has been made by the Secretary the holder has certain procedural protections. The Secretary may take action following the determination only after he has given the holder written notification and has provided him thirty days for action to resist the determination.[67] The Secretary must provide a written statement of the reasons for the determination and the notified holder may request an opportunity for an informal hearing.[68]

Export to Unlisted Countries

Export of a pipeline drug was illegal under the FDC Act before the 1986 Act came into effect. This Act provides for the export of pipeline drugs to listed countries with the Secretary s approval and affords an exporter of such drugs certain rights when exporting to an unlisted country If the Secretary determines that a pipeline drug is being exported directly or trans-shipped through a listed country to an unlisted country and that the import presents an imminent hazard to the public health in such a country the Secretary may immediately declare prohibition of the ex port of the drug to the importer [69] The Secretary must give the exporter prompt notice of that determination and provide an opportunity for an expedited hearing.[70] The Secretary s determination to prohibit the export cannot be stayed pending a final court order [71]

62. *Id.* § 802(b)(1)(A).
63. *Id.* § 802(b)(1)(D).
64. *Id.* § 802(b)(1)(E).
65. *Id.* §§ 802(b)(1)(G), 802(b)(2) (the holder also has to meet the reporting requirements of § 802(c)—notification of any withdrawal of an approval of the drug by any country to which it has been exported); 21 U.S.C. § 381(d)(1) (1982).
66. Drug Export Amendments Act of 1986, *supra* note 5, at § 802(e)(2).
67 *Id.* § 802(e).
68. *Id.*
69. *Id.* § 802(e)(3)(A).
70. *Id.*
71. *Id.* § 802(e)(3)(B). Export without the Secretary authorization remains punishable under the FDC Act, 21 U.S.C. §§ 355, 381(d) (1982), but the exporter may continue to export up to the time judicial proceedings end in conviction.

If the Secretary believes that a pipeline drug is being imported directly or through trans-shipment to an unlisted country but has not made, or cannot make, an imminent hazard finding, he can, subject to notice and hearing requirements, still prevent the ex port of such a drug.[72] If the Secretary believes the holder of an application for export is exporting the drug directly or indirectly to an unlisted country he may give such a holder sixty days to provide information relevant to the allegation and the opportunity for a hearing.[73] Upon the expiration of sixty days, the Secretary shall prohibit the export of the drug to an unlisted country provided that he has determined that export is taking place to an unlisted country [74]

If the Secretary receives "credible evidence" that an importer in a listed country is subsequently exporting from that country to an unlisted country he shall notify the holder of the NDA application of such evidence and require the holder to investigate the export of such imports. The holder must then report to the Sec retary within fourteen days of the receipt of such notice.[75] If the Secretary determines that the importer in a listed country has ex ported the drug to such an unlisted country he shall prohibit the holder from exporting the drug "unless the Secretary determines the export by the importer was unintentional."[76]

Export of Tropical Disease Drugs

There are many drugs for which sponsors will not pursue approval for U.S. sale because they are effective only in the prevention or treatment of diseases prevalent elsewhere. The FDC Act now permits drugs that are used in the prevention or treatment of tropical diseases and for which no NDA is pending to be approved if:[77]

1. The Secretary finds based on "credible evidence including clinical investigations that the drug is safe and effective in the importing country for the prevention or treatment of a tropical disease in that country

72. Drug Export Amendments Act of 1986, *supra* note 5, at § 802(e)(5).
73. *Id.*
74. *Id.*
75. *Id.* § 802(e)(6).
76. *Id.*
77 Drug Export Amendments Act of 1986, *supra* note 5, at § 802(f)(1). The term "tropical diseases" will have to be defined in guidelines or regulations issued by the FDA as it is not defined in the FDC Act.

2. the drug is manufactured, processed, packaged, and held in conformity with current good manufacturing practices and is not adulterated,[78]
3. the outside shipping package is labeled for export to certain authorized countries,
4. the drug is not subject to a notice that the manufacture is contrary to the public health and safety of the U.S., and
5. such requirements are met and comply with the specifications of the foreign purchaser the laws of the importing country the labeling and shipping requirements, and is for export only [79]

Sponsors of the export of drugs used for the prevention and treatment of tropical diseases must meet application and reporting requirements similar to those of the sponsors of the export of pipeline drugs to listed countries. In contrast to the sponsors of applications for export of pipeline drugs, these sponsors must demonstrate in their applications that there is "credible evidence including clinical investigations" that the drugs are safe and effective.[80] This wording seems to indicate that drugs affecting tropical diseases must be further along in the pipeline than those drugs seeking approval for export to listed countries. Pipeline drugs must have an IND to proceed with clinical trials but the results of clinical trials showing safety and effectiveness are not required. Sponsors of drugs affecting tropical disease are required to report to the Secretary the receipt of any information indicating that the drugs might not be safe and effective for tropical disease purposes.[81]

The Secretary may withdraw approval for the export of such drugs subject to notice and informal hearing requirements[82] if:

1. they do not meet the requirements for export outlined in 1 5 immediately above,
2. the sponsors have not reported, or
3. the manufacture of such drug for export is contrary to the public health and safety of the U.S.[83]

78. 21 U.S.C. §§ 351(a)(1), (a)(2)(A), (a)(3), (c), (d) (1982).

79. The complete requirements of this section are outlined in 21 U.S.C. § 381(d)(1) (1982). *See* text at n.29 for complete summary of 21 U.S.C. § 381(d)(1) (1982).

80. Drug Export Amendments Act of 1986, *supra* note 5, at § 802(f)(2)(C).

81. *Id.* § 802(f)(3)(A). They are also required to report any information indicating adverse reaction to any such drug. *Id.* § 802(f)(3)(B).

82. Drug Export Amendments Act of 1986, *supra* note 5, at § 802(f)(4)(A).

83. *Id.*

The Secretary may also withdraw approval for export if a determination is made that the drugs are either being trans-shipped[84] or exported directly[85] to a country for which the Secretary cannot make a finding regarding the safety and effectiveness of these drugs for the prevention and treatment of tropical diseases. Approval may also be withdrawn if the Secretary finds that these drugs present an imminent hazard to the public health in such country This determination cannot be stayed pending final court action. [86]

Where the Secretary receives "credible evidence" that the holder of an application is exporting the drug to a country where the Secretary cannot make a finding that the drug is safe and effective, the Secretary shall give the holder sixty days from the receipt of notice to provide information and an opportunity for an informal hearing on such evidence.[87] Upon expiration of sixty days, the Secretary shall prohibit the export of such drug to a country for which a finding cannot be made that it is safe and effective.[88] If the Secretary receives credible evidence that the holder of an NDA application is legitimately exporting to an importer who is then exporting to another country where the drug is not safe and effective, the Secretary will give notification to the holder and require an investigation of the allegation. A report must be received by the Secretary within fourteen days.[89] The Secretary shall prohibit the export if it is determined that there was an intentional trans-shipment by the importer [90]

Devices

There are thousands of medical devices, ranging from bandages to prosthetic implants. They are regulated by the Medical Device Amendments Act of 1976 (1976 Amendments) to the FDC Act.[91] "Device" is defined as any health care product that does not accomplish any of its intended purposes by chemical action in

84. *Id.* § 802(f)(4)(C).
85. *Id.*
86. *Id.*
87 *Id.* § 802(f)(4)(D).
88. *Id.*
89. *Id.* § 802(f)(4)(E).
90. *Id.*
91. The Medical Device Amendments of 1976, Pub. L. No. 94-295, 90 Stat. 539 (codified at 21 U.S.C. § 510(c)-(k) (1982)). *See also* 21 U.S.C. § 381(d)(1)–(2) (1982).

or on the body or through the metabolic process.[92] Products that work by such chemical or metabolic action, such as the contraceptive copper intrauterine device (IUD), fall under FDC Act regulation as drugs.

The FDC Act as amended permits the export of a medical device that has not been approved for domestic use provided that:

1. the device is in accord with the specifications of the for eign purchaser
2. use of the device does not conflict with the laws of the country to which it is intended to be exported,
3. the shipping package is labeled as intended for export,
4. the device is not sold or offered for sale in U.S. domestic commerce,
5. the Secretary has determined that export of the device is not contrary to public health and safety and
6. the device is approved by the health agency of the country to which it is intended to be exported.[93]

The FDA has authority to require that notification of exportation from the U.S. be given to the health agency of the importing country by manufacturers who are exporting medical devices not marketable in U.S. domestic commerce. In addition, the FDA is itself required to notify the importing country of potentially hazardous medical devices. The Deputy-Commissioner of the FDA testified in 1984 that experience with the administration of these provisions has been favorable.[94] The FDA processes from 250 to 300 export requests each year and has found the two most impor tant public health safeguards in the device export provisions to be the public health assurance and the approval of the importing country [95]

92. 21 U.S.C. § 321(r) (1982).

93. 21 U.S.C. § 381(d) (1982); *see generally* Stigi, Greathouse & Dunning, *The Food and Drug Administration Policy in Relation to the Exportation of Medical Devices*, 30 FOOD DRUG COSM. L.J. 193 (1983).

Note that section 381(d) does not clarify the expression contrary to public health and safety, while the 1986 Act explains that the manufacture has to be contrary to the public health and safety of the U.S., *see, e.g.*, Drug Export Amendments Act of 1986, *supra* note 5, at § 802(f)(1)(D).

94. *Drug Price Competition and Patent Term Restoration Act of 1984: Hearings on S. 2748 Before the Senate Comm. on Labor and Human Resources*, 98th Cong., 2d Sess. 5-36 (1984) (statement of Mark Novitch, M.D., Act. Comm'r of Food and Drug Administration).

95. *Id.*

Questions of Scientific Fact and Policy

Decisions regarding the acceptability of both drugs and devices will respond to factors that, in general terms, may be separated into the objective and the subjective. Objective factors may be described as scientifically factual, and include proven effectiveness of the drug or device on controlled populations, and side effects proven to be caused by the product. Scientific applications of a product to different ethnic populations may produce different results because of, for example, genetic, dietary and environmental reasons. The consequences of application are nevertheless objectively verifiable and replicable.

In contrast, subjective factors are judgmental responses to both objective and intuitive perceptions regarding whether a product is suitable for a target population. Whether the interaction of the proven side effects, effectiveness rates and proven disfunctional consequences of a product warrant the product s availability for a given population is a question of policy The policy expresses subjective assessments of policy makers and not a demonstrable calculus. Objective data will be decisive when they show failure to satisfy predetermined levels of effectiveness and safety However these levels are set subjectively and reflect perceptions of acceptable safety and effectiveness for a population. Such perceptions are molded by factual considerations of the seriousness and incidence of the condition intended to be treated and policy considerations on the degree of risk that is acceptable by society Accordingly the factual and policy components of a decision on approval of a therapeutic product are often distinguishable.

The distinction between scientific fact and scientific policy is a useful concept[96] in understanding drug approval and its effect on the export and import of pipeline drugs, even though at certain levels scientific interpretation or perception of fact may reflect policy determinations.

A policy decision to approve or disapprove a drug includes decisions based on both fact and the subjective considerations previously noted. However judgments based on scientific fact cannot deviate from the scientific pronouncement; for example, chemists seldom disagree about the scientific structure of a compound once it has undergone sufficient chemical analysis. On the

96. *See* McGarity, *Substance and Procedural Discretion in Administrative Resolution of Science Policy Questions: Regulating Carcinogens in EPA and OSHA*, 67 Geo. L.J. 727 729-747 (1980).

other hand, resolution of science policy questions requires the drug regulator to make decisions on policy grounds that the scientist has not been able to make on grounds of fact.

The "hard" sciences are distinguishable from the "soft" or social sciences, where "facts" or hypotheses tend to contain significant but often unstated policy and philosphical components. An example of a "science policy question" is whether to regulate human exposure at low doses to a substance that is proven carcinogenic at high doses. Animal studies quantify the carcinogenic ity of the substance at high doses but it may be impossible in practice to test enough animals to determine low-dose effects. The policy response to this problem has been to predict low-dose effects by extrapolating from high-dose effects, assuming a linear relation between dosage and response. However since it is by no means proven that the dose/response relationship is linear there has been much controversy surrounding the validity of low-dose estimates. A further delicate issue concerning animal studies is the extrapolation of all of these findings to humans, for instance the differences between species with regard to absorption, rate of metabolism, excretion, etc.

Answers to questions of scientific fact are universal. In contrast, scientific policy questions are answered by different countries in different ways. For instance, one country may decide to approve a drug even in the face of scientific uncertainties[97] because of the prevalence of the disease in that country By necessity each country must have its own health rationale for resolving science policy questions. While countries cannot doubt scientific evidence, they may legitimately examine the process by which agencies such as the FDA deal with science policy questions.

The determination of which drugs constitute a hazard involves resolution of questions both of scientific fact and of scientific policy New drugs and medical devices unapproved for U.S. domestic use may or may not prove hazardous. Any drug the FDA has not yet approved is presumed to be possibly hazardous. FDA reg-

97 Regulators cannot always postpone their decisions until definitive data is available but must often make decisions based on inferences from scientific data which is insufficient or subject to varying interpretations. Drug regulators need defined policy to guide them in determining: 1. whether to proceed even though the data is insufficient or uncertain, and 2. what kind of inferences can be drawn from such data, if the decision is in fact made to proceed; *see* Gelpe & Tarlock, *The Uses of Scientific Information in Environmental Decision Making*, 48 S. CAL. L. REV. 371, 371-427 (1974).

ulatory action taken after a drug or device has already been approved, such as recall, constitutes evidence that the drug or device is unsafe or ineffective.[98]

A suspicion that the drug or device may be hazardous may precipitate regulatory control at any point along the continuum of drug product regulation from initial testing to approval, manufacturing, packaging, labeling, storage and, finally use. The regulatory action may result in removal of the product from the market because of a demonstrated lack of safety or efficacy as based on evidence of scientific fact. For example, in 1974 the Dalkon Shield was removed from the market because of its lack of safety [99] The evidence that Dalkon Shields are unsafe is based on findings of scientific fact that are universal and therefore know no national boundary

Another kind of regulatory action consists of weighing the risks and benefits of a new drug that has successfully undergone initial testing within the health and social context peculiar to the U.S. For example, the FDA found the drug Depo-Provera unacceptable for use as an injectable contraceptive because, among other reasons, the FDA thought its risks outweighed its benefits in view of the alternative means of contraceptive protection available in the U.S.[100] This decision was based primarily on a determination of scientific policy The FDA assessed the evidence and decided the risk was inappropriate for this country In contrast, other regulatory agencies in countries with different contraceptive options to Depo-Provera have resolved this science policy question by accepting the risk and approving contraceptive use of Depo-Provera.

A drug regulatory authority s decision to release a drug for national use will have to conform to substantive and procedural rules of domestic law the latter tending in practice to be more detailed. When domestic authorities make decisions whose primary or secondary effects are known or intended to affect other

98. 21 U.S.C. §§ 355(e), 366 (1982).

99. Hutchins, Benson, Perkin & Soderstom, *The IUD After 20 Years: A Review*, 17 FAMILY PLANNING PERSPECTIVES 244, 252 (1985); *see also* Tatum & Connell, *A Decade of Intrauterine Contraception: 1976 to 1986*, 46 FERTILITY AND STERILITY 173-92 (1986); Van Dyke, *The Dalkon Shield: A "Primer in IUD Liabilty*, 6 W ST. U. L. REV. 1, 1-52 (1978).

100. Letter from Donald Kennedy, FDA Commissioner, to the Upjohn Corporation (July 25, 1978), *explained in The Depo-Provera Debate, Hearings before the House Select Committee on Population*, 95th Cong., 2d Sess. 302-314 (1978); Paxman & Potts, *Depo-Provera: Ethical Issues In Its Testing And Distribution*, 1 J. MED. ETHICS 1, 31-47 (1984).

countries, legal rules governing relations among different states must be taken into account when making policy determinations.

INTERNATIONAL PRINCIPLES APPLICABLE TO DRUG EXPORTS

There are at least three established and evolving international law principles that apply to the U.S. export of drugs and devices: the principles of State Sovereignty [101] State Responsibility [102] and, an aspect of the latter the observance of international minimum standards.[103] Not suprisingly there is constant tension between these principles. The sovereign right of a state to regulate its own nationals and control its own territory is often in conflict with the state s duty to exercise its rights in a manner consistent with its responsibilities not to unreasonably harm the interests of other states.[104]

101. In the Corfu Channel Case (Merits) (U.K. v. Alb.), 1949 I.C.J. 4, 35, 36 (April 9, 1949), the International Court of Justice held that Britain act of protectively minesweeping Albanian territorial waters that constituted an international strait was violation of Albanian sovereignty, notwithstanding Albania' negligence or delay in undertaking protection in its territory. *See also* Handl, *Territorial Sovereignty and the Problem of Transnational Pollution*, 69 AM. J. INT'L L. 50, 65 (1975).

102. It was held in Trail Smelter Arbitration (U.S. v. Can.), 3 R. Int'l Arb. Awards 1905, 1965 (1941), that Canada was responsible for the conduct of private smelting company which released fumes that caused crop and lumber damage in the United States. It has been observed that while the narrow holding of this case is limited to international pollution the case has been interpreted broadly to hold that nations have responsibility to ensure that activities within their territory do not cause damage in the territory of another state. Comment, *United States Export of Products Banned for Domestic Use*, 20 HARV. INT'L L.J. 331, 371 (1979). Similarly, the International Court of Justice held in the Corfu Channel Case (U.K. v. Alb.), 1949 I.C.J. at 22, that it is every state obligation not to allow knowingly its territory to be used for acts contrary to the rights of other states. *See generally* Christenson, *The Decline of Attribution in State Responsibility*, in INTERNATIONAL LAW OF STATE RESPONSIBILITY FOR INJURIES TO ALIENS 321 (R.B. Lilich, ed. 1983).

103. International Minimum Standards invoke State Responsibility by requiring state conduct which conforms to the standard habitually practised among civilized nations. Chevreau Case (Fr. v. Gr. Brit.), 2 R. Int'l Arb. Awards 1113 (1931), English Translation 27 AM. J. INT'L L. 153, 160 (1933). *See also* Neer Claim (U.S. v. Mex.), U.S. and Mexican General Claims Arbitration, 4 R. Int'l Arb. Awards 60, 61-62 (1926), which held that State Responsibility arises from an insufficiency of governmental action so far short of international standards that every reasonable and impartial man would readily recognize its insufficiency. Whether the insufficiency preceeds from deficient execution of an intelligent law or from the fact that the laws of the country do not empower the authorities to measure up to international standards is immaterial. *See infra* notes 121-24 for examples of the recently promulgated international guidelines that could become international minimum standards if "habitually practised. Chevreau Case, *supra*, at 1160; *see also* Handl, *State Liability for Environmental Damage*, 14 AM. J. INT'L L. 525, 529-31 (1980).

104. Magraw, *Transboundary Harm: The International Law Commission Study of International Liability*, 80 AM. J. INT'L L. 305, 308-09 (1986).

These principles are usually applicable only to states or international institutions themselves and not directly to individual nationals or private national enterprises. The legal applicability of such principles to private industry such as drug and device manufacture often varies according to their acceptance and the degree to which they are enforceable by countries internal courts. Primary responsibility for observance of international standards rests with national governments. Their failure to police and control national companies acting in violation of these standards renders them liable for their errors of omission under the international law doctrine of State Responsibility [105]

State Sovereignty

There are two aspects of state sovereignty affecting international trade in medical drugs and devices that are relevant to importing and exporting. Importing sovereignty empowers a country to tolerate or encourage reception into its territory of products coming from abroad. This reception of imports is permitted as the country thinks fit but is subject to the terms of its international obligations.[106] A country s willingness or wish to import an item, however cannot limit another country s sovereign power to control that item s exportation. Traditional international customary law of State Sovereignty recognizes the national right to limit and condition exportation.

The discussion of whether states should control acts *jure gestionis* (commercial acts) or confine themselves to acts *jure imperii* (strictly governmental acts) is of primarily historic interest. It is almost invariably accepted even in countries favoring a free-enterprise economy that control of exports is a proper use of state power whether on military strategic, economic, or for instance, humanitarian grounds.

A special challenge is posed in the medical drug and device field when a country bars exportation for the sole purpose of protecting ultimate consumers who are nationals of another country Although the humanitarian impulse appears benign and even praiseworthy the protection of individuals is primarily the responsibility of their national states. When one state monitors or

105. Trail Smelter Arbitration (U.S. v. Can.), 3 R. Int'l Arb. Awards, at 1965.

106. *See supra* text accompanying notes 102, 103 and *infra* text accompanying notes 116-137

supersedes another state s protection of its own resident nationals, it is an interference with that state s sovereignty Even when drugs or devices are known to be hazardous, a potential importing country may claim its sovereign right to make the critical decision regarding importation.

A country s acceptance of a drug depends upon a risk-benefit assessment which balances the foreseeable benefits and risks to a population due to the availability of the product with the foreseeable risks of nonavailability It may claim that no other country can make this assessment on its behalf and that each country bears the sovereign right and responsibility to make this assessment for its people. Furthermore, each country has the right to resolve questions of scientific policy based on its view of the needs of its own population, its disease patterns, and health ser vice delivery resources. Accordingly one country s resolution of science policy questions and its assessment of the comparative risk and benefit of a product is not necessarily relevant to another country's circumstances.[107] A drug that appears too hazardous in the U.S., such a the long-acting injectable contraceptive drug like Depo-Provera,[108] may present overcompensating benefits in another country where favorable alternatives are unavailable, too costly [109] or unsuitable for safe and effective self-administration by the patient.

International efforts have been undertaken to provide information to developing countries about the safety and effectiveness of drug imports. In 1977 the World Health Organization (WHO) established the Essential Drug List[110] in order to strengthen de veloping countries selection of proper use of drugs to meet their

107 It may be argued, however, that drug such as thalidomide is universally unacceptable in causing gross birth defects even if it can produce some degree of therapeutic benefit in patient populations.

108. *See The Depo-Provera Debate: Hearings before the House Select Comm. on Population*, 95th Cong., 2d Sess. 311 (1978). *See also* Paxman & Potts, Depo-Provera: Ethical Issues In Its Testing And Distribution, 1 J. MED. ETHICS 9-20, (1984).

109. In many countries the primary cost of therapeutic drugs is borne by national or other governmental health services; *see* Teff, *supra* note 3, at 604.

110. WHO defined essential drugs as "those considered to be of the utmost importance and hence basic, indispensable, and necessary for the health needs of the population. They should be available at all times, in the proper dosage forms, to all segments of society, WHA 28.66, Official Records of the WHO, 1975, No. 226, 35-6. *See also The Use of Essential Drugs*, World Health Organization Technical Report Series #685, (1983); *The Use of Essential Drugs*, World Health Organization Technical Report Series #722, (1985); Reich, *Essential Drugs: Economies and Politics in International Health*, HEALTH POLICY (forthcoming 1987) (discussion of WHO essential drug program).

needs. Notably it lists several drugs as essential, such as dehydroemetine and nifurtimox, which still remain unapproved by the FDA.[111] Additionally U.S. efforts could show more respect for other countries sovereignty by making all information it possesses regarding the operation of such drugs available to these countries, thereby leaving them free to make their own assessments regarding importation.

State Responsibility

A basic proposition of international law is that a state bears responsibility for emanations from its territory that cause harm in the territory of other countries, whether to the environment or land itself or for instance, to members of a national population.[112] State responsibility arises not only from positive acts attributable to a state,[113] but also from a state s failure to exercise appropriate control or regulation over private and corporate per sons acting in its territory in ways that may cause harm in other countries. Acts of commercial enterprises, whether private or state owned, are not normally attributed to the states in which they operate[114] but a state s international responsibility may arise when it fails to exercise control or due diligence necessary for the protection of international rights of others.[115]

111. *The Use of Essential Drugs*, World Health Organization Technical Report Series #722, at 17 20 (1985).

112. Corfu Channel Case (U.K. v. Alb.), 1949 I.C.J. 4, 22 (April 9, 1949); Trail Smelter Arbitration (U.S. v. Can.), 3 R. Int'l Arb. Awards 1905, 1965. State responsibility is based upon the general principle *sic utere tuo ut alienum non laedas*, *i.e.*, the duty to exercise one rights that do not harm the interests of other subjects of law. *See* Magraw, *supra* note 104, at 308. It has been defined:

> In any legal system there must be liability for failure to observe obligations imposed by its rules. Such liability is known in international law as *responsibility* A state is responsible, for example, if it fails to honour treaty, if it violates the territorial sovereignty of another state, if it damages the territory or property of another state or if it mistreats nationals of another state.

D.J. HARRIS, CASES AND MATERIALS IN INTERNATIONAL LAW 374 (3rd ed. 1983). The terms "state responsibility and "state liability are not necessarily interchangeable. Magraw, *supra*, at 316; *Symposium on State Responsibility and Liability for Injurious Consequences Arising out of Acts Not Prohibited By International Law*, 16 NETH. Y. B. INT'L L. XI (1985). *See generally* Handl, *supra* note 103, at 529; Note, *State Responsibility & Hazardous Products*, 13 CAL. W INT'L L.J. 116 (1983).

113. Christenson, *supra* note 102, at 326.

114. This includes situations in which they are state owned. *Id.* at 332.

115. For example, Switzerland agreed to pay damages to other countries for pollution of the Rhine due to its failure to have adequately controlled private Swiss chemical company activities. *See generally* Lewis, *Huge Chemical Spill in the Rhine Creates Havoc in Four*

It may not be evidence of an international legal responsibility that the U.S. regulates the export of hazardous products such as food products, pesticides and drugs. Responsibility may arise, however when information regarding hazards known to be associated with such products is not made available to potential importers, either through direct state notification or through an adequately enforced state requirement that producers make critical information available.[116] Direct notification by the state may be difficult because manufacturers submissions of research data, including contra-indications and toxicity levels, may be confidential and protected from disclosure by national law Drug companies, in particular may have produced such information at multimillion dollar expense and will jealously guard the information as a capital asset even when an application for approval fails. Relatively little more may have to be expended to achieve marketing approval and recovery of investments. If the state were to make such data internationally available it might be harmful to national industry [117] even though states have authority to enter into international agreements through which information in their possession may be shared (usually with due protection of commercial information).

Countries, N.Y Times, Nov. 11, 1986, at A1, col. 3. This incident demonstrates that nations do, in practice, acknowledge and accept the duty to prevent harm and then to compensate, if necessary. It likewise provides evidence that the duty is becoming *opinio juris* (state acceptance coupled with state practice), thus validating the existence of customary international law.

If state tried to invoke its own constitution or the absence of national legislation as defense to claim of international state liability for the export of dangerous product, it would have difficulty doing so successfully. *See* MOORE, HISTORY AND DIGEST OF THE INTERNATIONAL ARBITRATIONS TO WHICH THE UNITED STATES HAS BEEN PARTY 653 (1898) (discussion of *Alabama Claims Arbitration 1872*, where Great Britain was held liable for breach of its duty of neutrality during the U.S. Civil War through its failure to prevent private ship builder from exporting dangerous naval battle ships to the Confederacy, including *The Alabama*); *see also* Christenson, *supra* note 102, at 339-41 (discussion of inaction as an act of state).

116. *See* Corfu Channel Case (U.K. v. Alb.), 1949 I.C.J. at 22 (liability was imposed on Albania for its failure to notify, for the benefit of shipping in general, of "the existence of minefield in Albania territorial waters and in warning the approaching British warships of the imminent danger to which the minefield exposed them").

117 It is interesting to observe that the International Law Commission current consideration of international liability, which in part deals with state duty to give relevant and available information of harm originating from it has an exception for reasons of industial security. *See* Magraw, *Transboundary Harm: The International Law Commission Study of International Liability*, *supra* note 104, at 312, 327-29 (1986).

When a product is approved for marketing, either in the country in which it is manufactured or in another to which it is exported, all relevant information must be made available to governments health protection agencies and to prescribing physicians as well as to the intended ultimate consumers through labels and package inserts. An exporting state may bear a legal responsibility to ensure that its national exporters conform to appropriate standards of disclosure,[118] and perhaps to at least a uniform international minimum standard.

An interesting but unresolved issue is whether a state bears special responsibility to control export of drugs or devices known through domestic experience to be ultra-hazardous, such as the drug thalidomide.[119] Domestic law may apply principles of strict liability to domestic suppliers of ultra-hazardous products when injuries are caused by their products. Of course, this strict liability is based on the assumption that the supplier knew of the risk or ought to have known by exercise of due diligence. It is doubtful that state responsibility to exercise due diligence for the avoidance of such injury to other countries runs as far as a strict liability standard of care. However when domestic health protection authorities receive notice of harm, or at the least when they recall a product on grounds of harm, a duty may arise to prevent further exports or to ensure availability of appropriate information to other countries health protection authorities[120]either directly or through an international agency such as WHO

International Minimum Standards

The gradual development of international minimum standards of conduct that are applicable to all nations has increasingly limited both the exercise of sovereign rights and the discharge of state responsibility This development is seen in the international codes and agreements on minimum standards and guidelines of conduct in many fields, including health (e.g., the International

118. Corfu Channel Case (U.K. v. Alb.), 1949 I.C.J. at 22.

119. *See generally* Magraw, *supra* note 104, at 327-29; Jenks, *Liability for Ultra-Hazardous Activities in International Law*, 117 RECUEIL DES COURS 105 (1966 I).

120. In the Corfu Channel Case (U.K. v. Alb.), 1949 I.C.J. 4, 22 (April 9, 1949), the International Court of Justice guardedly found only that state may, up to certain point, be bound to supply particulars of the use made by it of the means of information and inquiry at its disposal" *see also* Magraw, *supra* note 104, at 327-28.

Code of Marketing of Breast Milk Substitutes, 1981),[121] the environment (e.g., the Stockholm Declaration, 1972),[122] economic matters (e.g., the New International Economic Order 1974)[123] and consumer protection (e.g., the United Nations Guidelines for Consumer Protection, 1985).[124] Although these international declarations are not legally binding, they are morally and politically persuasive and may provide a basis upon which future legal principles can be built. As these declarations become more specific and as countries begin to accept them and alter their practices accordingly they could, in time, become legally binding.[125]

The legitimacy of these standards is founded on provisions of the United Nations (UN) Charter calling for international cooperation to improve standards of living.[126] The UN Charter which became effective in 1945, was followed in 1946 by the adoption of the Constitution of the World Health Organization.[127] The WHO Constitution authorizes the World Health Assembly to adopt international regulations in specific health areas, including that of pharmaceuticals.[128] The World Health Assembly can also make recommendations that are not legally binding but are an important method of building an international consensus while leaving actual implementation to States.[129] An example of this kind of recommendation is the 1981 International Code of Marketing of Breast Milk Substitutes.[130]

Proposals have been made for a code on the international marketing of pharmaceuticals that would be similar to the Interna-

121. International Code of Marketing Breast Milk Substitutes, World Health Organization (1981). *See generally* Note, *Formulating Customary International Law: An Examination of the WHO International Code of Marketing of Breastmilk Substitutes*, 5 B.C. INT'L COMP L. REV. 377 (1982).

122. *The Stockholm Declaration, Report of the United Nations Conference on the Human Environment*, U.N. Doc. A/Conf. 48/14 (1972) *reprinted in* 11 I.L.M. 1416 (1972).

123. *The Declaration on the Establishment of the New International Economic Order* G.A. Res. 3201, 6 U.N. GAOR Supp. (No. 1) at 3, U.N. Doc. A/9556 (1974).

124. G.A. Res. 248, 39 U.N. GAOR Supp. (No. 10) at 179, U.N. Doc. A/39/10 (1985). *See* Mercial, *Consumer Protection and the United Nations*, 20 J. WORLD TRADE L. 206, 225 (March/April 1986).

125. *See supra* note 115 for discussion of *opinio juris*.

126. U.N. CHARTER art. 1(3), 55(B).

127 Constitution of the World Health Organization, *opened for signature* July 22, 1946, 62 Stat. 2679, T.I.A.S. No. 1808, 14 U.N.T.S. 185.

128. *Id.* arts. 21(d),(e).

129. *Id.* art. 23.

130. International Code of Marketing Breast Milk Substitutes, World Health Organization (1981).

tional Code of Marketing of Breast Milk Substitutes. These proposals include a 1978 World Health Assembly resolution requesting the WHO Director-General to investigate the development of a code of marketing practice for the pharmaceutical industry [131] Another proposal is the 1981 UN General Assembly resolution (entitled Exchange of Information on Banned Hazardous Chemicals and Unsafe Pharmaceutical Products), which requested the UN Secretary-General, and the relevant UN organs, to "establish an adequate system for monitoring the import of unsafe pharmaceutical products of doubtful therapeutic value. "[132] In response to a resolution passed by the 1984 World Health Assembly calling for the rational use of drugs,[133] a meeting of experts from governments, industry and consumer groups was held in 1985 to examine pharmaceutical marketing practices.[134] In 1986, at the Conference of Experts on Rational Use of Drugs, the Director-General of WHO reported that a group of experts will be convened to prepare WHO guidelines on minimum requirements for drug regulation and food labeling practices. [135]

WHO Certification Scheme

In 1975, the World Health Assembly of WHO established a Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce (Certification Scheme),[136] and set standards for a Good Practices in the Manufacture and Quality Control of Drugs Act (Good Manufacturing Practices Act).[137] The Certification Scheme recommends that the relevant authority of the exporting member state certify its exported pharmaceuticals by issuing a Certificate of Pharmaceutical Products. This certificate, issued at the request of the importing state, includes two assurances: 1) the exporting country has approved

131. W.H.A. Res. 31.32, 247 World Health Organization, Official Rec. 20 (1978).

132. G.A. Res. 166, 36 U.N. GAOR Supp. (No. 51) at 193, U.N. Doc. A/36/51 (1982).

133. Rational Use of Drugs, W.H.A. Res. 37.33, Thirty-Seventh World Health Assembly (1984).

134. *See Report of the Director-General to Thirty-Ninth World Health Assembly on the Conference of Experts on the Rational Use of Drugs, Nairobi (Nov. 1985)*, World Health Assembly A39/12 (Feb. 10, 1986).

135. *Id.* at 9.

136. *See* 226 World Health Organization, Official Rec. 88 (1975).

137 *Id., see* Cone, *International Regulation of Pharmaceuticals*, 23 VA. J. INT'L L. 332, 349-51 (1983).

the product for domestic sale, or if not, why and 2) the plant manufacturing the drug is subject to regular inspection and conforms to the standards established in the Good Manufacturing Practices Act.

The United States, along with at least one hundred other countries, participates in the Certification Scheme and thereby contributes to the application of appropriate testing standards and the use of adequate facilities. Furthermore, U.S. law requires that the manufacturers comply with the WHO's Good Manufacturing Practices Act.

Consistent with the principle of state sovereignty the relevant health authority of the importing country is provided with the information needed to make its own independent judgment whether to authorize domestic sale. If the importing country considers the certification procedure inadequate, it may apply to the exporting country for further information. This certification scheme thereby enables countries to import drugs without establishing their own expensive control and evaluation facilities. Although problems of relying on exporting countries are still present, importers can expect a degree of certainty in the quality of the imported drug.

Use of international standards may begin to alleviate the problems related to the variance in standards between countries. Nonetheless, the importer must still set its own threshold for quality and compare it with those standards recognized by the ex porter The success of any coordinating international agreement to ensure reliable quality in pharmaceuticals depends upon the voluntary compliance of its member states. In addition to U.S. participation in the WHO certification scheme, the U.S. regularly submits information on drugs and U.S. regulatory actions to the WHO for subsequent dissemination in the *WHO Drug Information Circular* and the *WHO Drug Information Bulletin*.

OPPOSING VIEWS ON EXPORT POLICY

In the debate in the past decade over the export of pipeline products, including drugs and devices, the positions taken by interested parties have fallen along a spectrum that runs from a paternalistic stance aimed to protect the "weak" to a position of strong sovereignty[138] aimed at maximizing a country s industrial

138. *See* Duby, *supra* note 1, at 422.

and exporting strength by requiring importing countries to protect their own nationals.

The advocates of paternalism rely on the state responsibility doctrine and international minimum standards to argue that the U.S. should not export products that are not approved for sale domestically They argue that to do otherwise would create a double standard of treatment between U.S. nationals and nationals of other countries by which products not good enough for U.S. residents can still be exported for sale to Third World populations.[139] Advocates of paternalism buttress their position by alleging a need to protect the health of U.S. nationals who travel abroad. Moreover it is explained that importing countries, especially those of the Third World, have inadequate drug regulatory control mechanisms.[140] In particular such advocates argue that many importing countries have neither the legislation required nor the enforcement mechanisms necessary to ensure the promotion and use of drugs only for the purposes they approve.

The proponents of respect for national sovereignty stress that the principles of both international comity and international law require respect for the rights of states to decide for themselves whether their nationals may use a particular drug, regardless of the regulatory status of that drug in the exporting country [141] They argue that it is a matter not of double standards, but of a standard that best enables countries to decide what medicines they will import on the basis of their own assessments of their own health needs, the diseases and health-related characteristics of their populations, the nature of their health care delivery systems, the availability of treatment alternatives and their own solutions to the risk-benefit equation. Proponents of this position argue that if an importing country wants to have the same approval standards as the exporting country it can simply adopt a country-of-origin rule, as many countries have. This rule allows the import of drugs only if approved for domestic use in the country of manufacture.

139. Criticism may not be of drugs *per se* but of the labeling and advertising used to promote them in other countries. *See* Yudkin, *Provision of Medicines in Developing Country*, THE LANCET, April 15, 1978, at 810.

140. *See* HOUSE COMM. ON GOVERNMENT, REPORT ON THE EXPORT OF PRODUCTS BANNED BY U.S. REGULATORS AGENCIES, H.R. Rep. 1686, 95th Cong., 2d Sess., at 27 (1978).

141. *See* Duby, *supra* note 1, at 424; *see generally* Phelps, *The New International Economic Order and the Pharmaceutical Industry*, 37 FOOD DRUG COSM. L.J. 200 (1982).

When issues of international health standards are considered, advocates of an approach favoring state sovereignty may make the limited concession to paternalism that it is better for the U.S. to have regulatory control over the export of domestically unapproved drugs than to have no control at all. Formerly U.S. drug manufacturers established subsidiaries in other countries from which new drugs, unapproved in the U.S., and perhaps also locally were nevertheless legally exportable to third countries. Such manufacturers thereby avoided the U.S. prohibition against export of pipeline drugs and evaded U.S. standards of consumer protection and information. Pursuant to the 1986 amendment of the FDC Act, U.S. manufacturers can export pipeline drugs from the U.S. without skirting regulatory prohibitions. However they are liable to controls which they may tolerate only in order to save the costs of funding foreign subsidiaries.

Opposing philosophies appeared polarized in Senate and House versions of the 1986 Act. A bill proposed by Senators Hatch and Quayle introduced into both the ninety-eighth[142] and ninety-ninth[143] Congresses was sympathetic to the export of pipeline drugs to requesting countries. The bill introduced by Congressman Waxman in the ninety-ninth Congress[144] was designed to limit export of hazardous drugs. Though different in orientation, the bills were not necessarily incompatible, and indeed both bore the seeds of the compromise that was achieved in enactment of the 1986 Act.

The Senate bill sought to promote export to informed countries of products that had not been shown harmful although they had not yet satisfied FDA standards. This bill reflected previous proposals to apply the same conditions to pipeline drug exports that had governed pipeline devices since 1976. Debated issues in

142. S. 2878, 98th Cong., 2d Sess. (1984); A House version of this bill, H.R. 3995 was introduced into the 99th Cong., 1st Sess., *reprinted in Hearing on Export of Unapproved Drugs Before the Subcomm. on Health and the Environment of the House Comm. on Energy and Commerce*, 99th Cong., 2d Sess. 20-40 (1986).

143. *The Pharmaceutical Export Amendment Act of 1986*, S. 1848, 99th Cong., 2d Sess. (1986). Another proposal, *The Drug Regulation Reform Act*, S. 2755, 95th Cong., 2d Sess. §§ 134-136 (1978); H.R. 11611, 95th Cong., 2d Sess. §§ 134-136 (1978), would have required permit for the export of all drugs, except those approved for domestic commerce; proposed procedures for the application, granting or denying of an export permit; and provided for cooperation with foreign governments through the exchange of information and training. *See* Comment, *U.S. Export of Products Banned for Domestic Use*, 20 HARV. INT'L L.J. 331, 339-41 (1979) (discussion of the 1978 Bill). *See also* Duby, *supra* note 1, at 421-22.

144. *The Hazardous Drug Export Prevention Act*, H.R. 3962, 99th Cong., 1st Sess. (1986).

the bill included the point at which the pipeline export could be permitted, which countries should be listed, and what different treatments should be given to requests for exports from listed and unlisted countries.[145]

Congressman Waxman s bill was seemingly motivated by a sense of the need to prevent U.S. companies from dumping drugs found unsafe by U.S. regulatory agencies in countries unaware of such determinations of unsafety It is notable that this bill proposed a provision requiring the completion of clinical studies and the filing of an NDA before export eligibility a smaller schedule of listed countries, and extraterritorial penal liability for U.S. companies whose practices abroad violated the FDC Act, such as mislabeling and false promotion.[146]

At a philosophical level, the opposing positions in the U.S. de bate on reducing or maintaining limits on the export of pipeline drugs centered on the sovereignty of other countries and the obligations felt in the U.S. to protect populations of other countries whose own means of protection were suspect. More mundane factors weighed in the balance, however that favored enactment of the 1986 Act. The sovereignty issue was addressed by Senator Hatch in 1985, when, as chairman of the Senate Committee on Labor and Human Resources that considered Drug Export Re form, he noted that:

> [t]he policy of the United Nations recognizes the right of all countries to have access to the full range of pharmaceuticals and places on the importing country the responsibility for protecting its consumers, with the technical assistance of foreign or international agencies where needed.[147]

145. *The Pharmaceutical Export Amendment Act of 1986*, S. 1848, 99th Cong., 2d Sess. (1986) (bill provided for mechanism to export unapproved new drugs to unlisted countries).

146. A provocative proposal to promote corporate responsibility for exported products is to legislate jurisdiction in U.S. company state of incorporation regarding injuries suffered by foreign consumers of foreign subsidiaries' products that are marketed in noncompliance with U.S. domestic quality control standards. For related discussion on the Bhopal disaster and the Union Carbide Corporation accountability, see generally Westbrook, *Theories of Parent Company Liability and the Prospects for an International Settlement*, 20 TEXAS INT'L L.J. 321 (1985).

147 *Drug Export Reform: Hearings Before the Senate Comm. on Labor and Human Resources*, 99th Cong., 1st Sess. 1-2 (1985) [hereinafter *Drug Export Reform Hearings*] (opening statement of Sen. Hatch).

UN Res. 137 provides: "Products that have been banned from domestic consumption and/or sale because they have been judged to endanger health and the environment should be sold abroad by companies, corporations, or individuals only when request for

However Senator Hatch went on to observe of the prevailing FDC Act that:

> [t]he U.S. ban does not really affect which pharmaceuticals reach foreign consumers, since any drug may lawfully be produced abroad, including in Soviet bloc countries and others, which do not recognize patent protection and may be marketed without restrictions around the world.[148]

Having negated the justification for the export prohibition on grounds of protection, the Senator pointed to the U.S. pharmaceutical industry s declining world position,[149] to which, he alleged, drug export restrictions had in part contributed. He quoted statistics indicating that passage of liberalizing legislation would result, over the next five years, in a $1 76 billion annual increase in exports, and an annual creation of 40,000 new jobs.[150] More conservative data anticipated annual export increases of $21 7 million and 2,482 jobs.[151] It was accepted that the true impact of new legislation would lie somewhere between these figures.

The argument of protective responsibility was urged in the House of Representatives, in the April 28, 1986 opening statement of Congressman Waxman, Chairman of the Subcommittee on Health and the Environment when the Subcommittee held hearings to consider the export of drugs.[152] Observing that the promises of new jobs and advantages to the U.S. balance of trade were attractive but no more than promises, Congressman Wax man cited findings that drugs removed from the U.S. market because of unsafety or ineffectiveness were sold overseas in countries lacking their own drug approval systems.[153] He found that proposed legislation to weaken controls on U.S. export law did not propose to remedy these problems with prevailing law but contained proposals that would make a troubling problem worse.

such products is received from an importing country or when the consumption of such products is officially permitted in the importing country. This resolution may be inapplicable to drugs denied approval not because of danger to health or the environment but because they offer no advance in country' existing health care resources. G.A. Res. 137 37 U.N. GAOR Supp. (No. 51) at 112, U.N. Doc. A/37/51 (1983).

148. *Drug Export Reform Hearings, supra* note 147 at 2.

149. *Id.* at 3.

150. *Id.* at 5.

151. *Id.*

152. *Hearings on Export of Unapproved Drugs, supra* note 142, at 1-2.

153. *Id.* at 1.

CONCLUSION

The 1986 Act was ultimately enacted through agreement and compromise among advocates of philosophically opposing views in Congress. Maintaining export prohibitions against drugs disapproved or withdrawn from the U.S. domestic market served protection advocates. Permitting regulated export of drugs actively progressing through the pipeline of FDA approval comparably respected foreign sovereignty and served the interests of the U.S. pharmaceutical industry and workforce.

By providing for the export of pipeline drugs to a number of other countries, the 1986 Act respects not only their sovereignty but also their capacity to discharge the responsibility to safeguard and advance the health of their populations. Management of the list of such countries is the responsibility of Congress.[154] Notably the present list is composed of the countries of Western Europe and Australia, Canada, Japan and New Zealand.[155] As a result, a wide measure of U.S. paternalism remains. The present list reflects the attitude that the majority of the world's countries containing the majority of the world's population are incapable of making a responsible risk-benefit assessment of drugs or the decision to import them, notwithstanding known or suspected hazards. The same attitude applies to the listed countries regarding drugs disapproved or withdrawn from sale in the U.S. The U.S. has remained unsympathetic to the perception of sovereignty that countries are responsible for their own import policies, with recourse to information and technical assistance from the U.S. and elsewhere if they choose to seek it.[156]

The seeming disadvantage suffered by unlisted countries might be mitigated if the Secretary had the power to treat all countries as listed countries for the purpose of drugs included in the WHO Essential Drug List.[157] The WHO with the expertise and experience available from FDA and elsewhere, should be relied upon to assess drugs as meeting health needs of Third World and other unlisted countries populations.

U.S. provisions prohibiting export of drugs disapproved in the U.S. not due to proven hazards but due to policy determinations

154. Drug Export Amendments Act of 1986, *supra* note 5, at § 802(b)(4)(B).

155. *Id.*

156. *See* discussion and Handl, *supra* note 101.

157 *See* discussion and sources *supra* note 110.

are problematic. A determination by the government that certain therapeutic alternatives are preferable supposes that government and bureaucrats know better than informed consumers how their therapeutic options are best exercised in their interests. Extended outside the U.S., this policy presents the appearance that such policy determinations are to be uniformly applied even though other countries have different resources and present their populations with different opportunities for choice. Risk-benefit assessments made for the U.S. are not necessarily appropriate for other countries. Such factors as national physicians to patient ratios and availability or acceptability of therapeutic options weigh differently in each nation s balance.

The U.S. could make the benefits of its pharmaceutical sophistication more widely available by expanding the exception the 1986 Act makes for tropical disease drugs to those drugs found necessary and effective in other countries, even though they are disapproved for use in the U.S. This would expand the availability of such drugs in a way similar to that done by the 1976 Amendment regarding the exportability of medical devices. The experience of the export of devices since 1976 may provide data on the effect of such a policy upon the U.S. balance of trade and employment as well as on resulting therapeutic benefit and harm.

These criticisms of the 1986 Act focus less on what it has achieved than on what it failed to achieve, due in part to the political compromises made to secure its passage. What was achieved in the 1986 Act is praiseworthy and better equips the U.S. to contribute beyond its borders to reduction of disease and promotion of health. In addition, it may be particularly important that the U.S. has not needlessly excluded itself from participation in world health developments and world markets in view of the imminence of biotechnological innovations.