Mutual Recognition Agreements and Harmonization[†]

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Food and drug law, a discrete specialty of American administrative law, increasingly involves international issues. At one time, these issues had a rather narrow range of motion and focused principally on long-standing import provisions[1] and legal aspects of "export policy" — should the United States allow exports only of products allowed here?[2]

Food and drug lawyers in both the government and private sectors, who once were able to spend most or all of their time concentrating on Food and Drug Administration (FDA or Agency) requirements and the U.S. regulatory scheme, find that global considerations increasingly influence their analysis of legal issues. In law schools, as well, courses such as "food and drug law" that are not part of the international and comparative law curriculum will delve more and more into issues that reach across national boundaries.

This Article focuses on two related topics in the internationalization of food and drug law: harmonization and agreements, including mutual recognition agreements (MRAs). It begins with a summary of how food, drugs, and medical devices are regulated in the United

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[1] *See* Federal Food, Drug, and Cosmetic Act (FFDCA) § 801(a), 21 U.S.C. § 381(a) (1994); *see also* Linda R. Horton, *The Food and Drug Administration's International Harmonization, Enforcement, and Trade Policy Activities* [hereinafter, *FDLI International Overview*], *in* 2 FUNDAMENTALS OF LAW & REGULATION: AN IN-DEPTH LOOK AT THERAPEUTIC PRODUCTS 101, 111, 131-35 (David L. Adams et al. eds., 1997) [hereinafter 2 FUNDAMENTALS]; Linda R. Horton et al., *International Harmonization of the Regulation of Drugs and Biologics* [hereinafter, *FDLI Drug Harmonization*], *in* 2 FUNDAMENTALS 437, 518-24.

[2] *See* FFDCA §§ 801(d), (e), 802, 21 U.S.C. §§ 381(d)-(e), 382 (1994); *see also* Horton, *FDLI International Overview* at 112; Horton, *FDLI Drug Harmonization* at 529-37; Linda R. Horton et al., *International Harmonization of Medical Device Regulations* [hereinafter, *FDLI Device Harmonization*], *in* 2 FUNDAMENTALS 555, 603-05. *See infra* notes 65-70 and accompanying text (discussing the FDA's authority over exports).

States by FDA. It continues with a discussion of FDA's philosophy and authority concerning harmonization and agreements, and concludes with an examination of the Agency's policies in these areas and recent and planned initiatives.

The United States and other countries have made remarkable progress in a short time in global harmonization activities for food, drugs, and medical devices. FDA's international harmonization activities comprise a wide variety of efforts to maintain and strengthen public health safeguards while striving toward common ground internationally on product standards, criteria for the assessment of test data, and enforcement procedures.

The recently completed MRA negotiation between the United States and the European Union (EU)[3] on drugs and medical devices[4] has generated much interest, and it provides a well-textured backdrop for a discussion of globalized food and drug law.

I.

A. *Globalization*

The shift to an international legal perspective in the food and drug law field reflects broad trends falling under the general rubric of "globalization." These trends have compelled FDA, as well as the industries it regulates and even consumer groups, to rethink their international strategies. Forces at work include:

- Economic globalization, evidenced by the growth of U.S. imports and exports; the increasingly international character of products and industries that FDA regulates; and World Trade Organization agreements;
- Public health globalization, and particularly the risk of cross-border spread of communicable diseases; and

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[3] The European Union (EU) is also known as the European Community. As of 1998, the EU comprises 15 countries, with another 10 or more hoping to join. Current members are Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, the Netherlands, Portugal, Spain, Sweden, and the United Kingdom.

[4] A summary of the Mutual Recognition Agreement (MRA) is appended to this article. On June 20, 1997, representatives of the United States and the EU initialed the agreement as an indication that the text was the one negotiated by the parties. Thereafter, each side initiated its required ratification procedures, including an FDA rulemaking as to drugs and devices. The parties signed the agreement on May 18, 1998, and exchanged letters on October 30, 1998, that triggered the entry into force of the MRA. *See infra* text accompanying note 151.

- The absolute certainty that available resources will not keep pace with the challenges presented by these trends.

Provisions of the World Trade Organization agreements encourage harmonization and serve as stimuli for MRAs. These include:

- The Agreement on Technical Barriers to Trade,[5] which encourages mutual recognition agreements (in which countries agree that exports will meet *importing* country's requirements), and
- The Agreement on the Application of Sanitary and Phytosanitary Measures[6] (referring to animal and plant health measures as well as human food safety measures), which encourages food safety control agencies to enter arrangements based upon a finding that the exporting country's laws are equivalent. Here, countries agree that exports will meet the *exporting* country's requirements after a finding by the importing country that the exporting country's requirements are equivalent to its own.[7]

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[5] Multilateral Trade Negotiations Final Act Embodying the Results of the Uruguay Round of Trade Negotiations, 33 I.L.M. 1125 (1994).

[6] WORLD TRADE ORGANIZATION, AGREEMENT ON THE APPLICATION OF SANITARY AND PHYTOSANITARY MEASURES (available at <http://www.wto.org/wto/goods/spsagr.htm>). A sanitary or phystosanitary measure is

> any measure applied: (a) to protect animal or plant life or health within the territory of the Member [a country or other entity, e.g., the EU, belonging to the World Trade Organization] from risks arising from the entry, establishment, or spread of pests, diseases, disease-carrying organisms, or disease-causing organisms; (b) to protect human or animal life or health within the territory of the Member from risks arising from additives, contaminants, toxins or disease-causing organisms in foods, beverages, or feedstuffs; (c) to protect human life or health within the territory of the Member from risks arising from diseases carried by animals, plants, or products thereof, or from the entry, establishment, or spread of pests; or (d) to prevent or limit other damage within their territory of the Member from the entry, establishment, or spread of pests.
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> Sanitary or phytosanitary measures include all relevant laws, decrees, regulations, requirements and procedures including, inter alia, end product criteria; processes and production methods; testing; inspection; certification and approval procedures; quarantine treatments including relevant requirements associated with the transport of animals or plants, or with the materials necessary for their survival during transport; provisions on relevant statistical methods, sampling procedures, and methods of risk assessment; and packaging and labeling requirements directly related to food safety.

Id. annex A, at 78.

[7] *See id.* art. 4.

B. *How Food, Drugs, and Medical Devices are Regulated in the United States*

FDA administers the Federal Food, Drug, and Cosmetic Act (FFDCA)[8] and several other laws, notably provisions of the Public Health Service Act.[9] The Agency has existed for more than a century.[10] It is our nation's only significant regulatory body for pharmaceuticals, medical devices, and cosmetics, and it is the principal regulatory body for foods.[11] FDA administers a national program, not one organized by or carried out through the states; however, the Agency does cooperate with state officials in a variety of productive ways.[12]

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[8] 21 U.S.C. §§ 321-397 (1994).

[9] *See* 42 U.S.C. §§ 241 (research and investigations), 242(a) (controlled substances), 242*l* (international cooperation), 262-263 (biological products), 264 (interstate and foreign infections disease control functions that relate to the law enforcement functions of FDA) (1994); *see also* 21 C.F.R. § 5.10(a) (1998).

[10] FDA's predecessor, the Bureau of Chemistry of the U.S. Department of Agriculture, began in 1862 with President Lincoln's appointment of a chief chemist. *See* FDA BACKGROUNDER (August 1995) (available at <http://www.fda.gov/opacom/backgrounders/miles.html>). The Bureau's first regulatory authority was enacted in 1890, 26 Stat. 414 (1890), followed 16 years later by the enactment of the landmark Food and Drugs Act of 1906, Pub. L. No. 59-384, 34 Stat. 768 (1906). *See* Act of Aug. 30, 1890, ch. 839, 26 Stat. 414; Food and Drugs Act of 1906, Pub. L. No. 59-384, 34 Stat. 768 (1906) The modern era of U.S. food and drug regulation is considered to begin with the 1906 law, which was replaced by the broader Federal Food, Drug, and Cosmetic Act of 1938, Pub. L. No. 75-717, 52 Stat. 1040 (1938). *See* Federal Food, Drug, and Cosmetic Act of 1938, Pub. L. No. 75-717, 52 Stat. 1040 (1938). In 1927, the name "Food and Drug Administration" was assigned to the Agency, Pub. L. No. 71-272, 46 Stat. 392 (1930), and in 1940 FDA was transferred from the United States Department of Agriculture (USDA) to the Federal Security Agency, the predecessor to today's Department of Health and Human Services. *See* Act of May 27, 1930, ch. 341, Pub. L. No. 71-272, 46 Stat. 392.

[11] Units of the U.S. Department of Agriculture have particular responsibilities for food regulation. In particular, the Food Safety and Inspection Service (FSIS), is the principal regulatory body for meat, poultry, and egg products. Also, the Environmental Protection Agency, an independent agency in the executive branch, registers pesticides and establishes tolerances for pesticides in food. FDA and FSIS enforce these tolerances.

[12] FDA may commission state officials to enforce the FFDCA. *See* 21 U.S.C. § 372(a) (1994). The individual states have significant activities involving food (particularly restaurants and other food service establishments) in cooperation with FDA and on their own. States regulate the practice of medicine and pharmacy and conduct significant health fraud activities. *See* Richard M. Cooper, *Introduction to Food and Drug Law and Regulation, in* FUNDAMENTALS OF LAW AND REGULATION: AN IN-DEPTH LOOK AT FOODS, VETERINARY MEDICINES, AND COSMETICS, 11, 12 (Robert P. Brady et al. eds., 1997) [hereinafter 1 FUNDAMENTALS]. States rarely try to take on the complex tasks of medical product approvals or inspection of manufacturing facilities. Concerning preemption, FDA-administered laws range from a general rule of preemption (as to devices, nonprescription drugs, and cosmetics, 21 U.S.C. § 360k (1994); 21 U.S.C.A. §§ 379r, 379s (West Supp. 1998)), to a mixed approach (as to food labeling and the drug requirements enacted in 1962 and codified in 21

FDA conducts its responsibilities not only through headquarters functions located in Washington, D.C., and its Maryland suburbs, but also through field offices all around the country. Establishment inspections are FDA's primary investigational technique. As discussed in more detail below, FDA conducts foreign inspections, particularly of manufacturers of drugs and devices, by sending investigators abroad on specific assignments.[13] FDA, however, does not post employees in other countries.

In general terms, food[14] and cosmetics[15] must be safe and properly labeled[16] and drugs and medical devices must be safe, effective,[17] and properly labeled.[18] Broadly, the Agency's activities include general regulations, approval requirements in certain areas, enforcement actions and voluntary compliance activities, and general information and education. FDA's regulations are found in Title 21 of the Code of Federal Regulations, and these are supplemented by numerous non-binding explanatory documents known generally as guidance documents.[19] FDA prides itself on its transparency, both through publications in the Federal Register and other publications, such as its monthly magazine, FDA Consumer. The Agency's Internet homepage[20] is also a rich source of information on the Agency, its requirements, and its guidance documents. Procedural regulations[21]

U.S.C. § 343-1 (1994)) to statutory silence and, therefore, treatment under general constitutional law and administrative law principles (food adulteration, biologics requirements) as illustrated in *Hillsborough County, Florida v. Automated Medical Laboratories, Inc.*, 471 U.S. 707 (1985). State laws may continue to provide traditional personal injury remedies involving FDA-regulated products, even where state regulation generally is preempted. *See* Medtronic v. Lohr, 518 U.S. 470 (1996).

[13] *See* Horton, *FDLI International Overview*, *supra* note 1, at 135.

[14] *See* 21 U.S.C. §§ 342, 346-348 (1994). It is actually shorthand to say that the requires a food to be safe. The statute achieves this safety requirement in a backhand way by providing that a food is deemed "adulterated" and, therefore, subject to enforcement action if it, inter alia, bears or contains any poisonous or deleterious substance that may render it injurious to health. *See id.* § 342(a)(1).

[15] *See id.* § 361(a).

[16] *See id.* §§ 343, 362. A product is "misbranded," and therefore subject to enforcement action, if it is not labeled in accordance with requirements under the statute. *See id.* §§ 343, 362.

[17] *See id.* §§ 351, 355; 21 U.S.C.A. § 360c-e (West Supp. 1998).

[18] *See* 21 U.S.C. § 352 (1994).

[19] *See* Federal Food and Drug Administration's Development, Issuance, and Use of Guidance Documents, 62 Fed. Reg. 8,961 (1997) (discussing the FDA's policy on these issues). The Food and Drug Administration Modernization Act of 1997 (FDAMA), Pub. L. No. 105-115, 111 Stat. 2296 amended section 701 of the FFDCA to codify FDA's policy on guidance documents and also to require the Agency to promulgate this policy as a rule. *See* 21 U.S.C. § 371 (1994).

[20] The Internet address for FDA is: <http://www.fda.gov>.

[21] *See* 21 C.F.R. pts. 10-16 (1998).

and public information[22] regulations assist the public in interacting with the Agency.

Good manufacturing practice (GMP) regulations have been issued for food,[23] drugs,[24] and medical devices.[25] GMPs are practices and procedures for manufacturing, processing, and packing these products to ensure their quality and purity. FDA investigators conduct both periodic and "for cause" inspections of manufacturers for compliance with GMPs. In the United States, failure to comply with FDA's GMPs results in an adulterated product[26] and can result in FDA enforcement action, or voluntary action, that bars both domestic shipments and entry of international shipments of affected products.[27]

GMP regulations are based on the premise that finished product testing cannot suffice and that safety and quality must be built into products. FDA's view is that it is impossible to assure that a food, drug, or medical device possesses whatever characteristics the law requires it to have — safety for all products, identity/potency for drugs, and adherence to product design specifications for devices — if there has not been attention to controls on raw materials and labels, sanitation of the site, hygienic practices of production workers, record keeping, lab tests to check in-process products at critical stages and to check finished products, and other steps set forth in FDA regulations and supplemented by the manufacturer's in-house procedures. Plainly, not all finished products can be tested and to do so would be to destroy the products. So, therefore, the processor must have in place controls that result, reliably, in the production of only those products that meet FDA requirements. In recent years, FDA investigators have paid particular attention to process validation, laboratory

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[22] *See id.* pt. 20.

[23] *See id.* pt. 110 (setting forth the current good manufacturing practice in manufacturing, packing, or holding human food). In addition, FDA has promulgated specialized rules on product processing in Title 21, Code of Federal Regulations, for certain food categories: dietary supplements (pt. 111), thermally processed low-acid foods packaged in hermetically sealed containers (pt. 113), acidified foods (pt. 114), fish and fishery products (pt. 123), and bottled water (pt. 129).

[24] *See id.* pt. 210 (Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; General); and pt. 211 (Current Good Manufacturing Practice for Finished Pharmaceuticals).

[25] *See id.* pt. 820 (1998) (Quality system regulation).

[26] *See* 21 U.S.C. § 351(a) (1994).

[27] *See* FFDCA § 301(a), 21 U.S.C. § 331(a) (1994) (prohibiting the introduction or delivery for introduction into interstate commerce of any adulterated or misbranded drug); FFDCA § 802(f)(1), 21 U.S.C. § 382(f)(1) (Supp. 1996) (prohibiting exportation of a drug if it is not manufactured, processed, packaged, and held in substantial conformity with good manufacturing practices (GMPs)).

operations, bulk pharmaceuticals, and microbial contamination, and FDA stresses these concerns in its work with other countries.[28]

FDA's principal remedies in cases of noncompliance[29] with GMPs and other requirements are in rem product seizures,[30] injunctions,[31] and criminal prosecutions.[32] FDA does not possess direct litigating authority but it brings cases in the federal courts through the Department of Justice.[33] Noncompliant imports are detained at points of entry, through a program of cooperation between FDA and customs officials of the Department of the Treasury.[34] For products such as new drugs[35] or certain medical devices[36] that are subject to approval requirements, denial or withdrawal of product marketing authorizations can be the means for enforcement. The Agency also has authority to undertake administrative embargoes of certain products believed by investigators to violate the law.[37] Also, civil money penalties may be assessed for certain violations, e.g., most violations involving medical devices.[38]

Much compliance occurs through voluntary actions by responsible firms, often with the Agency's strong encouragement. FDA has issued guidelines that govern recalls.[39] When products need to be removed from the market, voluntary recalls are the principal means. In some product areas — infant formula,[40] medical devices,[41] biologics,[42] and radiation-emitting electronic products[43] — FDA has

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[28] *See* Horton, *FDLI Drug Harmonization*, *in* 2 FUNDAMENTALS, *supra* note 1, at 508.

[29] Prohibited acts are listed in 21 U.S.C. § 331 (1994).

[30] *See id.* § 334.

[31] *See id.* § 332.

[32] *See id.* § 333.

[33] *See id.* § 335.

[34] *See id.* § 381.

[35] *See* 21 U.S.C. § 355 (1994).

[36] *See* 21 U.S.C.A. § 360c(a)(1)(C), 360e (West Supp. 1998).

[37] FDA possesses administrative embargo, or administrative detention, authority for devices, *see* 21 U.S.C. § 334(g) (1994) and, pursuant to authority shared with the USDA, for meat, poultry, and egg products, *see id.* §§ 679(b), 467f(b), 1031.

[38] *See id.* § 333(f). FDA has issued a procedural regulation governing its civil money penalty authorities. *See* 21 C.F.R. pt. 17 (1998). In this regulation, the Agency lists the statutory provisions that are governed by these procedures. *See* 21 C.F.R. § 17.1 (1998).

[39] *See* 21 C.F.R. pt. 7(C) (1998).

[40] *See* 21 U.S.C. § 350a(e)(1) (1994).

[41] *See* 21 U.S.C.A. § 360h(e) (West Supp. 1998); 21 C.F.R. pt. 810 (1998).

[42] *See* 42 U.S.C. § 262(d)(2) (1994). Biologics (e.g., vaccines, blood-derived products, and allergenic extracts) comprise a specialized category of medical products that are principally regulated under provisions first enacted in 1902, now found in section 351 of the Public Health Service Act, 42 U.S.C. § 262(d)(2) (1994), as well as relevant provisions of the FFDCA.

authority to order recalls. Even where FDA lacks authority to order recalls, it may issue binding regulations requiring record keeping and product coding that is needed for effective recalls.[44] In many cases, legal actions are obviated through some combination of warning letters and voluntary actions.[45]

Some products require FDA approval before marketing. Examples are new drugs[46] and certain medical devices.[47] Support for approval is marshaled through laboratory research, animal studies, and clinical investigations in human subjects done by product sponsors, not by FDA.[48] The information is combined in an application for FDA consideration under the relevant statutory and regulatory criteria. Often FDA guidance documents make suggestions about what kinds of tests are needed, and direct communications between FDA and product sponsors help assure that investigations are undertaken that will satisfy requirements.[49] Thus, FDA's work is not to test products as a prelude to market authorization, but to grant approval based upon the Agency's review of data generated in studies conducted by, or for, product sponsors. The Agency tests products only as part of its general surveillance responsibilities.

C. *FDA Authority over Imports*

Under FFDCA and other laws administered by FDA,[50] both domestic and foreign suppliers that furnish products to the U.S. market must meet the same requirements.[51] These requirements apply not only with respect to products themselves, but also to the conditions under which the products were processed or stored, as these conditions determine the characteristics of the products. Thus, foreign producers that ship to the United States, as well as domestic ones, are

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[43] *See* 21 U.S.C. § 360*ll* (1994).

[44] *See* National Confectioners Ass'n. v. Califano, 569 F.2d 690, 695 (D.C. Cir. 1978).

[45] *See* I. Scott Bass, *Enforcement Powers of the Food and Drug Administration: Drugs and Devices*, *in* 2 FUNDAMENTALS 55, 68-70.

[46] *See* 21 U.S.C. § 355 (1994).

[47] *See id.* §§ 360(c), 360(e).

[48] *See id.* §§ 355(i), 360j(g); *see also* Geoffrey M. Leavitt et al., *Human Drug Regulation*, *in* 2 FUNDAMENTALS 159, 160-66.

[49] As is discussed in the text, *infra*, accompanying notes 123-26, increasingly these guidance documents on testing requirements are being written in transnational international harmonization activities.

[50] Similarly as to biological products, the Public Health Service Act provides for inspections of all licensed firms, whether domestic or foreign. This provision dates back to 1902. *See* 42 U.S.C. § 262 (1994).

[51] *See* 21 U.S.C. § 381(a) (1994).

expected to maintain sanitary establishments: the FFDCA bars from U.S. commerce a food, drug, device, or cosmetic that is adulterated because it has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or it may have been rendered injurious to health.[52] This requirement is mentioned not only in the Act's adulteration provisions,[53] but also in its import provisions[54] — thus affording U.S. consumers the same protective provisions, with respect to the conditions under which imported products are processed or held, as apply to domestically produced products. Regardless of whether the insanitary conditions were here in the United States, in a processing facility in another country preparing products for export to the United States,[55] or in transit from there to here, the law prohibits the shipment in interstate commerce of adulterated or misbranded products.[56]

In sum, foreign firms are expected to meet the same product requirements and the same GMP regulations as domestic firms must meet.[57] Importing countries must concern themselves with the conditions of processing in the country of origin. An agency like FDA cannot test every import. Moreover, testing of product samples is useful in some areas, e.g., checking for illegal pesticide residues, but in most instances is not an effective way of looking for processing deficiencies that could result in hazardous product characteristics such as microbial contamination or subpotent or superpotent drugs.[58]

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[52] *See id.* Furthermore, foreign suppliers' compliance with device GMPs is specifically required. *See id.*

[53] *See id.* §§ 342(a)(4), 351(a)(4), 361(a).

[54] *See id.* § 381(a).

[55] *See id.* § 381. *Cf.* United States v. Food, 2,988 Cases, 64 F.3d 984, 986 (5th Cir. 1995) (discussing government seizing of imported canned Chinese mushrooms).

[56] *See* 21 U.S.C. §§ 331, 381 (1994).

[57] *See id.* § 381(a). The FDA Drug Export Reform and Enhancement Act of 1996, contains provisions that allow importation of certain ingredients that do not meet FDA requirements for inclusion in products for export only. *See* FDA Drug Export Reform and Enhancement Act of 1996, Pub. L. No. 104-134, 110 Stat. 1321-313 (1996).

[58] Also, testing at a country's borders adds costs to imports and can result in loss of perishable goods that may ultimately be found to comply with the FFDCA. Often there are no test methods, or only slow or cumbersome methods, to detect microbial contaminants in food. Recently, as part of the Administration's Food Safety Initiative, the President sent to Congress proposed legislation to strengthen FDA's authority over imported food. This bill would give FDA explicit authority to deny entry to food from a country whose regulatory system does not provide for a level of protection provided in the United States. The legislation has been introduced in the House of Representatives by Representatives Eshoo and Pallone, *see* Safety of Imported Food Act of 1997, H.R. 3052, 105th Cong., and in the Senate by Senator Mikulski, *see* Safety of Imported Food Act of 1998, S. 1707, 105th Cong.

D. Foreign Inspections

Related to the issue of import control at the border is foreign inspection. FDA conducts inspections of foreign manufacturers as well as domestic firms, particularly as to drugs and devices. The President's Food Safety Initiative will result in some increase in international inspections and related activities, such as technical cooperation and assistance in the food area. At present, however, drug and device inspections comprise almost all of FDA's foreign inspections. In recent years, the number of foreign inspections involving drugs has increased significantly, from 156 in 1992 to nearly 500 in 1995. The resources devoted to all foreign inspections have also increased, from eight full-time equivalents in 1992, to 47.5 in 1996. As mentioned earlier, the FFDCA applies equally to the products of domestic and foreign drug manufacturers. The Agency's authority to deny entry to imported products that "appear" to be adulterated, misbranded, or in violation of the new drug provisions[59] has been interpreted as enabling the Agency to deny entry to products produced in facilities (or in countries) that have denied FDA investigators the right of inspection.

Over the years, FDA has conducted inspections of approximately 4,200 firms in seventy-two different countries. Traditionally, most inspections have been in European countries, although a significant number occur in Canada, China, Japan, Thailand, Mexico, Malaysia, and Korea. FDA conducts these inspections in response to applications or submissions from or involving foreign firms[60] and investigations of complaints or recalls. The Agency also conducts routine and follow-up inspections.[61] As in the case of domestic inspections, foreign inspections involve discussions with firms' management, responses to deficiencies, inspection observations,[62] detailed written reports, and review by FDA headquarters offices. However, unlike FDA's traditional domestic inspections, which have not been preannounced, foreign inspections occur only after FDA has provided prior notice to the firm to be inspected. FDA's foreign inspectors, in most cases, are senior investigators who are technically experienced and competent in their fields, able to work independently, capable of

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[59] *See* 21 U.S.C. § 381 (1994).

[60] The foreign firm is either the applicant or the source of the bulk drug identified in an application. In the United States, as well as in other countries, foreign firms are a significant source of bulk drugs.

[61] FDA conducts some inspections if a foreign firm has made a bid to supply products or is a supplier to the U.S. military.

[62] FDA uses a form known as FDA-483 to record inspectional findings.

handling difficult situations, and diplomatic. The typical foreign inspection trip lasts three to four weeks, with two to five inspections per trip, and covers more than one country.

In the area of drugs, a foreign inspection often involves one or more of the following areas: administrative information, raw materials (handling, storage, controls, etc.), production operations (standard operating procedures, validation, production records, packaging and labeling, facilities, equipment, and maintenance), and product testing (procedures and methods). If any type of official FDA action results against the foreign firm, the action usually consists of automatic detention of the firm's products or disapproval of the relevant application or submission.

In June 1997, FDA issued a report on foreign inspections. This report was the product of a Task Force directed by the Deputy Commissioner for Operations. The report made several recommendations for approaches that FDA could use to evaluate the status of foreign establishments that manufacture products for import into the United States:

- Use of risk-based criteria for prioritizing the foreign firms that will be inspected;
- Implementation of the new Field Accomplishment and Compliance Tracking System, which will contain one combined Official Establishment Inspection for all foreign and domestic firms, comparable with other systems, and will provide the regulatory history of each firm;
- Providing information to U.S. customers regarding the status of products on Import Alert via direct mailings, Internet, and publication in the Federal Register;
- Continuing efforts to improve communications with the public health components of foreign governments in an effort to broaden inspectional information exchange; and
- Implementing a statistically based sampling program using a risk-management strategy built on criteria that will help target resources on products that are most likely to fail inspection.

Although FDA conducts foreign inspections, and will continue to do so, FDA and its counterparts in foreign countries are striving to harmonize regulatory requirements, to engage in cooperative regulatory activities such as joint training and inspections, and to look for ways to rely upon one another's efforts, e.g., by exchanging inspectional results. Because resources for FDA's foreign inspection program will never be sufficient to provide the degree of inspectional coverage for foreign processors commensurate with programmatic

needs, FDA needs to increase these international activities. That need should be kept in mind in connection with the later discussion on the subject of agreements.

E. Exchange of Information About Inspections

FDA shares information about its inspections through a variety of formal and informal arrangements. First, much information about FDA inspections is public and is shared with other countries upon request. Second, even non-public information can be shared, provided the requirements in FDA's regulations are met.[63] Third, through the Compliance Status Information System (COMSTAT), discussed below, certain countries have arranged for direct access to an FDA computerized database that includes information as to whether U.S. and foreign firms inspected by FDA are in compliance with GMPs. Last, but not least, FDA enters into Memoranda of Understanding (MOUs) and MRAs with other countries in order to enhance cooperation, sharing of compliance information, and reliance upon inspections by foreign counterparts.

COMSTAT, developed in the early 1970s as a computerized database on the current GMP status of pharmaceutical and medical device manufacturers, repackers, assemblers, contract sterilizers, and control testing laboratories, now includes information on some 20,000 firms that FDA has inspected in the United States or abroad.

Originally aimed at providing timely information to U.S. procurement agencies about manufacturers' compliance status, COMSTAT also assists FDA headquarters and other government agencies to assess quickly the GMP compliance status of a firm. COMSTAT is a profile class-oriented system not a product-specific system. In other words, in providing GMP compliance status information, COMSTAT does not provide information on each product a manufacturer makes, but rather categorizes pharmaceuticals and medical devices into broad categories, such as drug dosage forms, and provides compliance status information based on available inspection information.

In addition to U.S. government agencies, the drug approval authorities in Australia, Canada, and Denmark are able to access the COMSTAT database directly. The foreign agencies are able to obtain only publicly available information through this direct access, under FDA's regulation on sharing non-public information with for-

[63] *See* 21 C.F.R. pt. 20 (1998), particularly § 20.89.

eign officials, although follow-up inquiries could yield needed information not available to the public.[64]

F. FDA Authority over Exports

FDA's authority extends to exports,[65] but is more limited than is the case for domestically produced products and imports. A food, drug, or medical device that meets the requirements of the FFDCA, and thus is eligible for commercial distribution within the United States, generally may be exported without any FDA approval or involvement.[66] As to a product intended for export that could not otherwise be commercially distributed within the United States because it would be considered either adulterated or misbranded, the general rule is that the product may nevertheless be exported if it: "(A) accords to the specifications of the foreign purchaser, (B) is not in conflict with the laws of the country [of destination], (C) is labeled on the outside of the shipping package that it is intended for export, and (D) is not sold or offered for sale in domestic commerce."[67] Thus, in a nutshell, the exporter shipping products from the United States must comply either with FDA's laws or with the laws of the importing country.

Additional requirements apply to the export of unapproved new drugs, biologics, and medical devices subject to pre-market approval application requirements. The law differentiates between exports of unapproved products to highly developed countries listed in the FFDCA,[68] which are minimally regulated, and those destined for other countries.[69] Although the FDA Export Reform and Enhance-

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[64] *See id.* § 20.89.

[65] For a discussion of FDA's authority over exports, see Horton, *FDLI Drug Harmonization, in* 2 FUNDAMENTALS, *supra* note 1, at 524-36, 602-05.

[66] *See* 21 U.S.C. §§ 381-382 (1994).

[67] *Id.* § 381(e).

[68] *See* 21 U.S.C.A. § 382(b) (West Supp. 1998). Listed countries are Australia, Canada, Israel, Japan, New Zealand, Switzerland, South Africa, and the countries of the EU and the European Economic Area (EEA). *See id.* At the time the FDA Export Reform and Enhancement Act became law, there were 15 countries in the EU. *See* FDA Export Reform and Enhancement Act, Pub. L. No. 104-134, 110 Stat. 313. The EEA countries were the EU countries, Iceland, Liechtenstein, and Norway. Note that, because section 382(b)(1)(A)(i) of the FFDCA refers to the EU and EEA, rather than their individual members, the ranks of the listed countries will automatically expand as nations accede to the EU or join the EEA.

[69] *See* 21 U.S.C. § 382 (1994). The export provisions of the FFDCA were overhauled in the FDA Export Reform and Enhancement Act of 1996, Pub. L. No. 104-134, 110 Stat. 1321-313 (1996) *amended by* Pub. L. No. 104-180, 110 Stat. 1569 (1996). *See generally* Linda R. Horton, *Ethics and Trade: Exports of Unapproved Pharmaceuticals and Medical Devices*, 15 MED. & L. 649 (1996).

ment Act,[70] passed in 1996, made significant changes in these requirements, this law retained a provision requiring unapproved drug exports, and device exports under that provision, to meet GMPs. In the context of an MRA, it obviously is important for FDA to possess the legal authority needed to enforce compliance by U.S. exporting firms with GMPs.

G. *Features of Other Countries' Regulatory Systems Relevant to Harmonization and Agreements*

In many countries, GMPs and inspections are an essential part of the control of food, drugs, and medical devices. In other countries, as in the United States, an additional food safety control system known as Hazard Analysis Critical Control Points[71] is being widely adopted.[72]

Inspections are recognized as an essential component of a drug regulatory system by member states of the EU and other countries. The EU's legal basis for inspection is laid down in several laws and guidelines.[73] The European Commission is responsible for the harmonization of inspection procedures and technical matters, the European Agency for the Evaluation of Medicinal Products is responsible for coordinating national inspections and pharmacovigilance, and the "supervisory authorities" in the member states are responsible for conducting inspections of manufacturers located within their

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[70] Pub. L. No. 104-134, 110 Stat. 1321-313 (1996), *amended by* Pub. L. No. 104-180, 110 Stat. 1569 (1996).

[71] Hazard Analysis Critical Control Points (HACCP) is a scientific, preventive approach to food safety. To develop and maintain a HACCP system, a food producer identifies both the significant hazards posed by a product and process and what preventive or control measures must be put in place to control those hazards. A decision as to whether a hazard is significant depends on both the likelihood of occurrence and the severity of the hazard if it were to occur. Next, the producer identifies the "critical control points," the points in the process where significant hazards can be controlled, as well as the critical limits for the preventive measures for each such point. HACCP also contemplates requirements that the food producer have in place systems for monitoring, record keeping, assurance that the system is working through testing and other means, and corrective actions. For further discussion, see Frederick H. Degnan, *The Regulation of Food Safety*, 1 FUNDAMENTALS, *supra* note 12, at 161, 175-76. *See also* Phillip C. Olsson & Dennis R. Johnson, *Meat and Poultry Inspection: Wholesomeness, Integrity, and Productivity*, 1 FUNDAMENTALS, *supra* note 12 at 205, 230-31. The author is indebted to the latter authors' summary of HACCP.

[72] HACCP has been required for seafood, 21 C.F.R. pt. 123 (1998), and for meat and poultry, 61 Fed. Reg. 38, 806 (1996).

[73] *See* Council Directive 75/319, *amended by* Council Directive 89/341, 1989 O.J. (L 142) 32; *see also* Council Directive 91/356, 1991 O.J. (L 193) 34; Council Regulation 93/2309, 1993 J.O. (L214) 36.

borders.[74] In the EU, inspection is ordinarily conducted by a qualified individual employed by the responsible agency in the country where the facility is located, but the inspection is on behalf of the EU as a whole, not simply that member state.[75] For imported drugs, batch testing by a qualified person in the member state where the product enters is contemplated, although foreign inspections can also be conducted when requested by a member state, the European Agency for the Evaluation of Medicinal Products, or the European Commission.[76] Three member states (U.K., Germany, and France) have done foreign inspections.[77]

Although it is the opinion of the author that no other country has a drug or medical device approval system as rigorous as that of FDA, a convergence of regulatory controls of drugs and medical devices is occurring on such basics as GMPs, international product standards, and adverse event reporting. For pharmaceuticals, harmonization and technical cooperation activities by the World Health Organization over the past half century have resulted in widespread consensus on these basics as well as product identity and quality requirements, basic registration to control what is on the market, labeling, and GMPs.[78] Testing guidelines are also now being harmonized, as discussed below. Not all countries are attempting to maintain full-fledged approval systems; others rely upon certificates or other evidence of marketing eligibility in the United States and other countries.[79] What sets FDA apart from the drug approval authorities of other economically developed countries is its interest in scrutiny, not only of summaries of investigations, but also of the studies themselves,[80] including the clinical reports themselves in many cases.

For medical devices, FDA maintains a government-based approval system with a small proportion of devices requiring full-blown Pre-market Approval Applications, a fairly large proportion requiring

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[74] *See* Karin Bredal Jensen, National Board of Health, Denmark, *Good Manufacturing Practice Inspection in Europe, In Light of the New Central Agency and Current International Agreements*, 29 DRUG INFO. J. 1211, 1211-16 (1995).

[75] *See* Philippe Meyer, European Commission, *The Future GMP Inspection System (Inside and Outside the European Community): What Does it Really Mean?*, 28 DRUG INFO. J. 977, 979 (1994).

[76] *See* Jensen, *supra* note 74, at 1212-13.

[77] *See id.* at 1213.

[78] *See* Horton, *FDLI Drug Harmonization*, *supra* note 1, at 451-53.

[79] *See* WORLD HEALTH ORGANIZATION, GUIDING PRINCIPLES FOR SMALL NATIONAL DRUG REGULATORY AUTHORITIES, 3 WHO DRUG INFORMATION 43 (1989).

[80] *See* Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research, FDA, Address at the Meeting of the Center for Drug and Evaluation Research's International Activities Advisory Committee (Aug. 7, 1998).

pre-market notifications or "510(k)s," and a substantial number of the simpler devices exempted from both approval and pre-market notification. The review of the 510(k) looks principally at whether the device is substantially equivalent to one marketed already. The main competing paradigm is the medical device regulatory system in the EU, which includes vesting pre-market approval authority in conformity assessment bodies (CABs), many of them in the private sector, known as "Notified Bodies."[81] These bodies are hired by sponsors and are responsible for reviewing products and ascertaining compliance with EU laws. The regulatory authorities in health ministries of member countries of the EU retain key responsibilities other than product approval — particularly in naming the bodies that are eligible, and in conducting post-market surveillance.

In 1995, FDA announced its interest in experimenting with the use of "third-party" review bodies for medical devices.[82] The FDA Modernization Act of 1997 (FDAMA)[83] codified and expanded FDA's pilot program.[84] Under both the pilot program and FDAMA program, FDA decides which devices are eligible,[85] selects the eligible participating bodies through an accreditation process, and makes final approval decisions in all cases on devices.[86]

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[81] The term "Notified Body" is based upon the fact that each EU member country is required to notify the European Commission of all Conformity Assessment Bodies found to possess the technical competence to carry out conformity assessment functions under the relevant EU directive.

[82] *See* THE WHITE HOUSE, NATIONAL PERFORMANCE REVIEW, REINVENTING DRUG AND DEVICE REGULATIONS 5, 20-21 (1995). FDA announced its pilot program in the Federal Register of April 3, 1996. *See* 61 Fed. Reg. 14,789 (1996).

[83] Pub. L. No. 105-115, 111 Stat. 2296 (1997).

[84] During the early stages of Congressional consideration of the legislation that became FDAMA, Congress considered adoption of a system more closely linked to the EU system. A General Accounting Office report during consideration of FDAMA was probably influential in the adoption of a more limited use of third-party "Accredited Persons," as now found in 21 U.S.C.A. § 360m. *See* GENERAL ACCOUNTING OFFICE, MEDICAL DEVICE REGULATION: TOO EARLY TO ASSESS EUROPEAN SYSTEM'S VALUE AS MODEL FOR FDA (1996).

[85] The devices that were eligible for the pilot study represented those whose reviews are in the intermediate range of complexity: they were not the lowest risk devices exempted from 510(k)s, nor were they the devices that due to novelty, risk, or similar factors must be the subject of Pre-Market Approval Applications or FDA-reviewed 510(k)s.

[86] *See* 21 U.S.C.A. § 360m (West Supp. 1998). FDA published a draft guidance on this program in the Federal Register of May 22, 1998. *See* 63 Fed. Reg. 28,392 (1998). Related draft guidance on the implementation of the sectoral annex on medical devices of the United States-EU MRA was published on July 2, 1998. *See* 63 Fed. Reg. 36,240 (1998).

II.

A. *Recent Changes in FDA's Authority for International Activities: FDAMA*

FDAMA made several changes in the law relevant to international harmonization and agreements. First, FDAMA placed harmonization policy squarely in FDA's statutory mission statement, which before FDAMA included two broad goals: (1) timely action on the marketing of regulated products, and (2) protecting the public health by assuring that foods and cosmetics are safe and properly labeled, that human and veterinary drugs are safe and effective, and that there is reasonable assurance of the safety and effectiveness of devices.[87] With FDAMA, FDA is given a third objective of "participat[ing] through appropriate processes with representatives of other countries to reduce the burden of regulation, harmonize regulatory requirements, and achieve appropriate reciprocal arrangements."[88] Both the original two goals and the new one are, "as determined to be appropriate by [FDA, to be carried out] in consultation with experts in science, medicine, and public health, and in cooperation with consumers, users, manufacturers, importers, packers, distributors, and retailers of regulated products."[89]

Second, FDAMA added new provisions to an internationally-oriented, medical device-specific section that had been added to the FFDCA in 1990 by the 1990 Safe Medical Devices Act.[90] The FDAMA provisions require FDA to "regularly participate in meetings with representatives of other foreign governments to discuss and reach agreement on methods and approaches to harmonize regulatory requirements"[91] and to

> support the Office of the United States Trade Representative, in consultation with the Department of Commerce, in meetings with

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[87] *See* 21 U.S.C. § 393(b)(1)-(2) (1994).

[88] 21 U.S.C.A. § 393(b)(3) (West Supp. 1998).

[89] *Id.* § 393(b)(4).

[90] Pub. L. No. 101-629, 104 Stat. 4511 (1990). The Safe Medical Devices Act added section 803 to the FFDCA, which established an Office of International Relations (codified at 21 U.S.C. § 383(a) (1994)) and provided that, "In carrying out the functions of the office . . . [FDA] may enter into agreements with foreign countries to facilitate commerce in devices between the United States and such countries consistent with the requirements of [the FFDCA]." 21 U.S.C. § 383(b) (1994). "In such agreements, the Secretary shall encourage the mutual recognition of — (1) good manufacturing practice regulations [for devices], and (2) other regulations and testing protocols as [FDA] determines to be appropriate." *Id.*

[91] 21 U.S.C.A. § 383(b)(3) (West Supp. 1998).

> representatives of other countries to discuss methods and approaches to reduce the burden of regulation and harmonize regulatory requirements if [FDA] determines that such harmonization continues consumer protections consistent with the purposes of this Act.[92]

Third, FDAMA carried over FDA's authority for entering into cooperative arrangements with other countries on drug and device inspections[93] and on device MRAs.[94] Also, FDAMA added to the law a provision on agreements with the EU in particular: the provision requires FDA to

> support the Office of the United States Trade Representative, in consultation with the [Department] of Commerce, in efforts to move toward the acceptance of mutual recognition agreements relating to the regulation of drugs, biological products, devices, foods, food additives, and color additives, and the regulation of good manufacturing practices, between the EU and the United States.[95]

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[92] *Id.* § 383(c)(1). Congress exempted dietary supplements from the new directives concerning harmonization and agreements. Congress had concerns that harmonization of U.S. regulatory approaches for these products — the subject of a deregulatory statute known as the Dietary Supplement Health and Education Act of 1994 — could result in a tightening of regulatory requirements in the U.S. if FDA were to follow the lead of countries that regulate vitamin and mineral products as drugs. *See* Dietary Supplement Health and Education Act of 1994, Pub. L. No. 103-417, 108 Stat. 4325. This 1994 statute "clarif[ied] that dietary supplements are not drugs or food additives, that dietary supplements should not be regulated as drugs, and that burden of proof is on the Food and Drug Administration . . . to prove that a product is unsafe before it can be removed from the marketplace." S. REP. No. 103-410, at 2 (1994).

[93] *See* 21 U.S.C.A. § 360(i) (West Supp. 1998). 21 U.S.C.A. § 360(i)(3) states that, "[FDA] is authorized to enter into cooperative arrangements with officials of foreign countries to ensure that adequate and effective means are available for purposes of determining, from time to time, whether drugs or devices manufactured, prepared, propagated, compounded, or processed by an establishment [in any foreign country engaged in the manufacture, preparation, propagation, compounding or processing of a drug or device that is imported or offered for import into the United States], if imported or offered for import into the United States, shall be refused admission on any of the grounds set forth in section 381 (a) of this title [on imports]." 21 U.S.C.A. § 360(i)(3) (West Supp. 1998). This provision was recodified as new subsection (3) of section 381 (a) as part of amendments that, for the first time, require all foreign drug and device manufacturers to register. Before, registration with FDA was optional for foreign firms. However, even before this change in the law, all firms, domestic and foreign, had to file product lists with FDA. *See* 21 U.S.C. § 360(j) (1994).

[94] *See* 21 U.S.C. § 383(b) (1994); *see supra* note 90 for text of 21 U.S.C. § 383(b).

[95] 21 U.S.C.A. § 383(c)(2) (West Supp. 1998). As noted in footnote 93, dietary supplements are exempt from this provision.

Additionally, FDAMA required FDA, within 180 days of the enactment of the law, to make public a plan for a framework for achieving mutual recognition of GMP inspections.[96]

Finally, two changes facilitated international harmonization and agreements in the devices area. A simple process for recognition of international device standards was provided,[97] and, as discussed earlier, FDA's third-party pilot program for device reviews was codified in the FFDCA.[98]

B. FDA Authority for International Activities: Harmonization

Harmonization authority is not a separate and mysterious mandate, but is part and parcel of the Agency's general authority for regulations, approvals, enforcement, and other activities. International activities that are consistent with the statutes the Agency administers and that support the Agency's purposes, may be undertaken by FDA, under the product-specific provisions of the law as well as general mandates such as the Agency's broad rulemaking authority under section 701(a) of the FFDCA.[99] For example, FDA can undertake rulemaking that brings its regulations in line with an international standard, so long as the resulting regulation is consistent with applicable statutes. Thus, international harmonization in the United States is achieved by use of the same processes, under the Administrative Procedure Act[100] and Agency administrative procedure requirements,[101] for issuance of harmonized rules and guidance documents as those that govern other Agency policy making. When FDA wishes to accept an international standard, rulemaking is required in some instances, while in others harmonization is achieved through identical or similar guidance documents. For example, FDA used rulemaking under a long-established statutory process[102] to adopt an internationally recognized quality systems approach in its medical

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[96] *See id.* § 383(c)(4); *see infra* notes 159-61 and accompanying text for this plan.

[97] *See* 21 U.S.C. § 360d(c) (1994). FDA made use of this provision through a draft guidance document listing a large number of device standards used by FDA reviewers. *See* 63 Fed. Reg. 9,561 (1998). Nomination of other standards for use by FDA was invited, and FDA recently published an expanded list of recognized standards. *See* FDA Modernization Act of 1997: Modifications to the List of Recognized Standards, 63 Fed. Reg. 55,617, 55,619 to 55,630 (1998).

[98] *See* 21 U.S.C.A. § 360m (West Supp. 1998); *see also supra* notes 84-86.

[99] *See* 21 U.S.C. § 371(a) (1994).

[100] 5 U.S.C. §§ 551-706 (1994).

[101] FDA's rules on administrative practices and procedures are set forth in 21 C.F.R. pts. 10-17 (1998).

[102] *See* 21 U.S.C. § 360j(f) (1994).

device GMP regulations.[103] However, where a binding requirement is not needed to fulfill public health objectives, e.g., most harmonized guidelines on drug testing, FDA publishes a draft guidance document in the Federal Register for public comment. After considering comments, within the Agency and in concert with international partners, FDA publishes a final guidance document in the Federal Register. An illustration of this process is the International Cooperation on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), discussed below.

C. *FDA Authority for International Activities: Agreements with Regulatory Counterparts in Other Countries*[104]

As with FDA's harmonization authority, discussed above, FDA's authority to enter agreements with foreign government agencies derives in part from a broad reading of the FFDCA and other statutes that FDA administers. Section 801 on imports allows decisions on imports to be made on the basis of examination of samples "or otherwise."[105] To the extent that an MOU with another country helps FDA to protect channels of commerce from violative products, the Agency's general authority to prevent violations also comes into play.[106] Furthermore, FDA possesses broad authority under several sections of the Public Health Service Act that also authorize agreements with other countries: section 301 (granting broad authority for public health cooperation); section 307 (authorizing international cooperation); section 351 (controlling biological products, most of which are also drugs or medical devices, e.g., certain in vitro diagnostic products and tissue-derived devices); and section 361 (authorizing regulations to control communicable disease).[107] FDA has additional, product-specific authority to enter MOUs on food, drugs, and devices.[108] As discussed in this Article, FDAMA added to

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[103] *See* 21 C.F.R. pt. 820 (1998).

[104] An FDA regulation, 21 C.F.R. § 20.89 (1998), allows FDA to give and receive confidential information with counterparts, without that information becoming available to the general public. For an interesting discussion of confidentiality of business information, see generally James T. O'Reilly, *Implications of International Drug Approval Systems on Confidentiality of Business Secrets in the U.S. Pharmaceutical Industry*, 53 FOOD & DRUG L.J., 123 (1998).

[105] *See* 21 U.S.C. § 381(a) (1994).

[106] *See, e.g.*, United States v. Food, 2998 Cases, 64 F.3d 984 (5th Cir. 1995).

[107] *See* 42 U.S.C. §§ 241, 242*l*, 262, 264 (1994).

[108] *See, e.g.*, Pesticide Monitoring Improvements Act of 1988, 21 U.S.C. §§ 1401-1403 (1994). This act directs FDA to enter into cooperative agreements with the governments of countries that are the major sources of food imports into the United States, subject to pesticide residue monitoring by FDA for the purpose of improving

the Agency's authority to enter into agreements as well as harmonization activities.[109]

International law and domestic law both come into play with respect to international agreements. Under both, what is important is the substance of the document rather than the name put on it (or its form, i.e., contract form versus exchange of letters). International law, in particular the law of treaties, has evolved over many centuries and has been codified in the Vienna Convention of the Law of Treaties. Although the U.S. Senate has not ratified the Vienna Convention, it is very influential in the interpretation of international agreements in the United States. The Vienna Convention by its terms applies only to binding international agreements; it is nevertheless referred to in the interpretation of agreements whether or not they are binding. When the U.S. State Department clears agreements with other countries, as discussed below, one of the main things it reviews is whether an agency is entering a commitment under international law and whether the agency has authority for the agreement in question, be it binding or non-binding.

Under U.S. law, there are four categories of international agreements:

- Treaties that must be ratified by a two-thirds vote of the Senate;
- Executive-legislative agreements that, due to statutes or custom are, after negotiation by the executive branch, the subject of legislation that must be passed by both houses of Congress by a simple majority, then presented to the President for his signature (trade agreements fall in this category);
- Presidential agreements under the President's constitutional powers, such as his powers as Commander-in-Chief, without need for Congress to enact legislation (this is a small category that is quite controversial with the Congress); and
- Executive branch agreements that are negotiated and entered under an agency's statutory authority (the category that is by far the most numerous).

FDA's agreements fall into the latter category, executive branch agreements, the authority for which derives from the statutes it administers, principally the FFDCA and the Public Health Service Act.

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ability to assure compliance with the pesticide tolerance requirements of the FFDCA with respect to imported food. *See id.* § 1402. As to drugs and devices, section 510(I)(3) of the FFDCA includes explicit provisions for agreements with other countries. *See* 21 U.S.C.A. § 360(i)(3) (West Supp. 1998).

[109] *See* 21 U.S.C. §§ 383, 393 (1994).

FDA's agreements with regulatory counterparts are typical of the agency-to-agency agreements that are dominant in today's world of "technical diplomacy." FDA clears its proposed agreements with foreign counterparts with the Department of State, under procedures governing clearance of Agency agreements known as the Circular 175 process. The legal basis for this process is the State Department's need to comply with a statute, the Case-Zablocki Act,[110] which requires the State to inform the Congress of executive branch agreements with other countries that were not submitted to the Senate as treaties for ratification under the U.S. Constitution.

Most FDA agreements are not binding. Usually neither FDA nor the foreign counterpart wants an agreement that has mandatory language in it. Furthermore, the U.S. Department of State generally looks for, and strikes out, mandatory language unless it is satisfied that the Agency possesses the authority to enter into an agreement with such language and intends the international commitment being undertaken. As with agreements of all sorts, FDA's non-binding agreements bond the participants in a joint venture toward mutually beneficial goals: this is their value.

Recently FDA has negotiated several agreements that include binding provisions: The MRA signed with the EU in 1998, discussed below, is a good example. FDA's authority under its statutes to enter into non-binding agreements is long-established. The Agency's authority to enter into binding agreements is a relatively new issue. Both FDA's Office of Chief Counsel and the State Department have cleared the MRA with the EU, on the basis that the same authority that empowers FDA to enter into non-binding agreements with regulatory counterparts also authorizes entering into binding ones.

The inclusion of binding features has implications under domestic administrative law. An agreement that binds an agency such as FDA may need to be the subject of notice-and-comment rulemaking.[111] One view is that FDA has the authority to enter into binding

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[110] 1 U.S.C. § 112b (1994), implemented at 22 C.F.R. pt. 181 (1998).

[111] *Cf.* Richard A. Merrill, *FDA and Mutual Recognition Agreements: Five Models of Harmonization*, 53 FOOD & DRUG L.J. 133, 135 (1998); David A. Wirth, *International Trade Agreements: Vehicles for Regulatory Reform?*, 1997 U. CHI. LEGAL F. 331, 331 (1997). Wirth explained:

> As more and more domestic regulatory issues concerning environment and public health become "internationalized" through trade agreements, as they have, it is only reasonable to expect a degree of . . . legal culture surrounding those issues domestically. If the Executive Branch does not undertake such an initiative on its own, then Congress, which has the exclusive, expressly enumerated constitutional authority to regulate international trade, ought to address the need by statute.

agreements with other regulatory counterparts in other countries, provided that the Agency goes through notice-and-comment rulemaking on the basis that the agreement and aspects of it constitute "binding norms" with respect to FDA.[112] FDA published the MRA with the EU in the Federal Register in the form of a proposed regulation, seeking public comment,[113] then as a final regulation that is codified in the Code of Federal Regulations.[114]

An alternative theory is that international agreements, even executive branch agreements under Agency statutory authority, are a separate species of decision than rules, orders, or other products of U.S. administrative procedure and do not need to be subject to a notice-and-comment process. There is some support for this view in *International Brotherhood of Teamsters v. Pena*,[115] in which the Teamsters union brought an unsuccessful challenge to a Department of Transportation finding that Mexican truck drivers' licenses are equivalent to U.S. licenses.

What is the practical consequence of the distinction between a binding and non-binding agreement? In the context of agreements on food, drugs, and devices, probably not much. The practical reality is that, in contrast to commercial contracts between buyers and sellers of goods, there is not a "world FDA" or even a world court empowered to hear the kinds of disputes that could arise under FDA agreements. If FDA were to lose confidence in the ability of an MOU partner to abide by the terms of the agreement, what FDA is likely to do is to return to the relationship that it had with that partner before the agreement. For example, if it is an agreement on the exchange of inspection reports on GMPs, where the Agency believes that the quality or thoroughness of the inspection or the resulting report is not at the level expected, FDA might cease to rely on the foreign partner's inspections and resume or increase its inspections in that country.

A provision included in 1994 as part of the Uruguay Round Agreements Act, the implementing legislation for the World Trade Organization agreements, requires notice and comment on FDA findings that another country's "sanitary or phytosanitary measure," e.g., a country's seafood safety inspection system, is equivalent.[116] The

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Id. at 368.

[112] *See* Community Nutrition Inst. v. Young, 818 F.2d 943, 949 (D.C. Cir. 1987).

[113] *See* 63 Fed. Reg. 17,744 (1998). *See supra* note 86 for additional notices relevant to the sectoral annex one medical devices.

[114] *See* 21 C.F.R. pt. 26 (1998).

[115] 17 F.3d 1478 (D.C. Cir. 1994).

[116] *See* Uruguay Round Agreements Act, Pub. L. No. 103-465, 108 Stat. 4809

provision, however, does not apply a similar notice-and-comment requirement as to agreements in other areas of FDA regulation. Where Uruguay Round notice-and-comment process applies, FDA must undertake either rulemaking or a Federal Register notice, with opportunity for comment, whenever FDA makes a finding that another country has an equivalent food safety measure. The law requires that rulemaking be used for a determination of the equivalence of a foreign country's measure to a United States "measure that is required to be promulgated as a rule under the [FFDCA] or other statute administered by [FDA]" and provides for use of a simple notice as to a determination of equivalency of a foreign measure to a United States "measure that is not required to be promulgated as a rule under the [FFDCA] or other statute administered by [FDA]." Whether the process followed is a proposed rule or a notice, the applicable standard is whether the foreign measure provides at least the same level of sanitary or phytosanitary protection as the comparable federal measure. FDA must provide an opportunity for interested persons to comment on the proposed determination and not issue a final determination on the issue of equivalence without taking into account the comments received.

One may ask, if FDA was already obliged to undertake notice-and-comment rulemaking before finding another country's food law to be equivalent, why was it necessary for Congress to include this requirement in the Uruguay Round Agreements Act? Or did Congress believe itself merely to be codifying an existing APA requirement? Most likely, Congress, in enacting this provision, was merely carrying out what it thought was the right policy outcome, i.e., that the public should have the opportunity to participate in decisions affecting its food supply, without focusing on whether the requirement was new or a restatement of prior law.

FDA's view is that the Uruguay Round Agreements Act rulemaking requirement does not apply when an MOU merely records an understanding between FDA and a foreign counterpart that producers in each country will simply *comply* with the other country's requirements. Under this approach, FDA has signed a non-binding cooperative arrangement with the New Zealand seafood authorities.[117] This agreement consisted not of an equivalence determination, but of reciprocal statements as to compliance. FDA would not

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(1994); 19 U.S.C. § 2578a (1994).

[117] These authorities are the Ministry of Agriculture and Forestry and the Ministry of Health of New Zealand. The agreement was signed on December 20, 1995, and published in the Federal Register. *See* 61 Fed. Reg. 7,112 (1996).

need to subject to notice-and-comment a finding that another country's system is *not* equivalent, any more than FDA is expected to use rulemaking when it declines to initiate any other process leading toward a decision when there is no requirement for such a decision.[118]

D. Authority for Mutual Recognition Agreements

References to MRAs in U.S. law are found in the Trade Agreements Act[119] as well as in the FFDCA.[120] The phrase "mutual recognition agreements," or "MRAs," has several meanings, but generally means either reliance upon one another's conformity assessment system or, where such reliance is not practicable, exchange of the results of conformity assessments to assure that the receiving country's requirements are met.

The European usage of "MRA" was heavily influenced by its internal market harmonization activities as aided by the European Court of Justice interpretation of the Treaty of Rome. Mutual exchange of conformity assessment results was a key part of a new European approach designed to facilitate the free flow of goods

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[118] A useful analysis is offered by Richard A. Merrill. *See* Richard A. Merrill, *FDA and Mutual Recognition Agreements: Five Models of Harmonization*, *supra* note 111, at 135. Professor Merrill postulates five models for FDA international agreements: (1) the agent-in-place model, in which a trading partner agrees to provide FDA with the results of its work ("This kind of international agreement raises the fewest problems with respect to the substantive requirements that FDA administers, and the fewest issues of administrative process."); (2) the enforcement discretion agreement, in which FDA agrees it will monitor less closely the products of a country whose domestic regulatory requirements FDA considers reliable; (3) the "deputy sheriff" model, in which FDA commits — unconditionally or conditionally — to accept the results of another country's efforts to verify compliance with FDA's requirements, with U.S. law as the law being applied; (4) the "equivalence" model, in which the United States agrees to accept another country's requirements as equivalent to FDA's requirements; and (5) the harmonization model, in which both sides need to change regulatory requirements to achieve a common approach. Professor Merrill finds rulemaking unnecessary for the first three models but probably necessary for the latter two. *See id.* at 136.

[119] 19 U.S.C. § 2541 provides in pertinent part:

> The Trade Representative has responsibility for coordinating United States discussions and negotiations with foreign countries for the purpose of establishing mutual agreements with respect to standards-related activities. In carrying out this responsibility, the Trade Representative shall inform and consult with any Federal Agency having expertise in the matters under discussion and negotiation.

Trade Agreements Act of 1979, 19 U.S.C. § 2541 (1994), *amended by* Uruguay Round Agreements Act, Pub. L. No. 103-465, 108 Stat. 4809 (1994).

[120] The FDA "mutual recognition" agreement authority is found in 21 U.S.C. § 383 (1994); *see also* 21 U.S.C. § 394 (1994).

within the EU through the mutual recognition of the results of tests.[121]

MRAs among conformity assessment bodies are becoming commonplace. A host of public and private sector entities, such as bodies that accredit laboratories, are entering into MOUs and MRAs with one another on conformity assessment practices. Generally, these relate to either the recognition of the results of product testing and quality system audits, or the exchange of reports from such testing or audits. Whether these agreements among non-governmental conformity assessment bodies have any effect upon regulatory agencies depends upon the laws of each country in which such a body operates and whether the government has given official status to such a body or the agreements it enters. This issue is becoming an important one, due to the trend toward increased use of private sector conformity assessment activities. In the United States, as to activities in the FDA-regulated sector, these agreements have no official standing unless FDA is a party to the agreement or otherwise provides for these agreements to have some official status through a process such as rulemaking or guidance documenting in which those affected by such a decision have an opportunity for comments.

E. FDA Harmonization Policy

Even before FDAMA added explicit harmonization provisions to FDA's statutory mandate, the Agency had published a harmonization policy on World Standards Day, 1995,[122] that summarized the Agency's activities and thinking on this subject.

F. Harmonization: Drug Regulation

FDA's principal harmonization activity for drugs, the International Conference on Harmonization (ICH), is a highly successful program that harmonizes requirements and guidelines for testing drugs and biologics.[123] ICH is an example of how FDA has joined with counterparts in other countries to write harmonized guidelines that protect the public and benefit industry by reducing duplicative testing.[124]

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[121] *See* Horton, *FDLI Device Harmonization*, *supra* note 2, at 582.

[122] *See* 60 Fed. Reg. 53,078 (1995).

[123] *See* Horton, *FDLI Drug Harmonization*, *supra* note 1, at 444-51 and articles cited therein.

[124] *Id.* This chapter includes a matrix showing the dates of FDA publication of proposed and final International Cooperation on Harmonization (ICH) documents. *See id.* at 446-50.

FDA's regulatory partners in ICH are the Commission for the European Communities (European Commission), the European Medicines Evaluation Agency, EU member country regulators, and Japan's Ministry of Health and Welfare. Industry participants are the European Federation of Pharmaceutical Industries Associations, the Japan Pharmaceutical Manufacturers Association, and the Pharmaceutical Research and Manufacturers Association of the United States. The ICH Secretariat is administered in conjunction with the International Federation of Pharmaceutical Manufacturers Associations in Geneva, an international non-governmental organization. Official observer status in ICH has been given to the World Health Organization (WHO), the European Free Trade Association, and the Health Protection Branch of Canada.

ICH has carried out its activities through large public meetings, in each odd-numbered year, since 1991. ICH also uses an intense schedule of continuous guideline-draftings by representatives of the six ICH members, with approximately fifty working groups (Expert Working Groups) that meet during peak work periods several times each year. Generic drug manufacturers recently began to participate in ICH meetings regarding guidelines and topics that could affect their interests.

The work products of ICH created in these working groups have consisted of a series of consensus guidance documents. These documents, after successive ICH steps of review and acceptance, including an opportunity for public review and comment in each jurisdiction, are forwarded to the regulatory agencies with the expectation that they will be formally adopted by the agencies. The premise of ICH is the harmonization of testing and of a core portion of the "dossiers," or written submissions. The countries that employ ICH guidelines, however, maintain separate approvals rather than negotiating MRAs on drug approvals. [125]

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[125] Particularly as the EU moves toward an internal system for mutual recognition of approvals, and ICH achieves success in harmonizing a considerable portion of the technical documents required for drug approval, the issue of mutual recognition of product approvals, as opposed to mutual recognition of GMPs, will arise more and more. For discussions of the issue of recognition of approvals within the EU and at the international level, see Horton, *FDLI Drug Harmonization*, *supra* note 1 at 470-73. Under current law, FDA lacks authority to recognize other countries' approval systems, as approval authority is vested in the Secretary, 21 U.S.C. § 355 (1994), and by delegation, FDA, 21 C.F.R. § 5.10 (1998). Furthermore, FDA policies disfavor a change in the law to enable such recognition. "With regard to the European Community, I believe that we should continue to standardize our requirements, but . . . it should be up to each country to decide in the end whether a drug should be approved or not." *Revitalizing New Product Development From Clinical Trials Through FDA*

The other major area of pharmaceutical harmonization relevant to the present discussion — and also relevant to the discussion later in this article of the MRA with the EU — are GMPs. Internationally, the WHO, in 1969, endorsed GMP requirements for drugs as consisting of "internationally recognized and respected standards," and WHO has revised those requirements on several occasions.[126] These WHO GMPs were modeled upon FDA's drug GMPs. A recent FDA analysis by the Center for Drug Evaluation and Research confirmed this similarity as to written requirements. A current priority is increasing harmonization as to compliance and enforcement.[127] Also, FDA's rulemaking to clarify its GMPs with respect to validation requirements[128] may necessitate a re-review as to whether the WHO's GMPs — and those of the EU[129] and other U.S. trading partners — remain equivalent to FDA's.

Furthermore, the EU does not yet apply GMPs to bulk drugs,[130] a shortcoming that will impede progress in implementing the drug GMP MRA with the EU, but that issue is being addressed.

Bulk drug GMPs for active pharmaceutical ingredients (APIs) are a current harmonization priority, with a new initiative in ICH that attempts to unify disparate activities on this topic in FDA, the EU, WHO, PIC/S,[131] APEC,[132] and ICH.[133] Underlying this interest is the recognition that, due to the increasing international commerce in bulk pharmaceutical chemicals for use in drug manufacturing, ade-

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Review: Hearing on S. 1477 Before the Committee on Labor and Human Resources, 104th Cong. 14 (1996) (statement of former Commissioner Kessler).

[126] *See* WORLD HEALTH ORGANIZATION, TECHNICAL REPORT SERIES NO. 863, WHO EXPERT COMMITTEE ON SPECIFICATIONS FOR PHARMACEUTICAL PREPARATIONS 155 (1996).

[127] *See PDA Interviews FDA's Stephanie Gray*, PDA NEWSLETTER, Sept. 1995, at 1.

[128] *See* 61 Fed. Reg. 20,104 (1996).

[129] *See* Council Directive 193/30, 1991 O.J. 83-86 (laying down principles and guidelines of good manufacturing practice for medicinal products for human use).

[130] Bulk drugs are sometimes called "starter materials," and generally the interest is in focusing attention upon *active pharmaceutical ingredients* (APIs).

[131] The Pharmaceutical Inspection Cooperation Scheme (PIC/S) is a cooperation program that originated as an international agreement, the Convention for the Mutual Recognition of Inspection in respect of the Manufacture of Pharmaceutical Products, commonly known as the Pharmaceutical Inspection Convention or PIC. Most participants are European. Australia is also a member, and FDA representatives participate actively in PIC/S.

[132] APEC is a governmental forum comprised of 21 Pacific Rim member economies: Australia, Brunei, Canada, Chile, Chinese Taipei, Hong Kong, Indonesia, Japan, Malaysia, Mexico, New Zealand, Papua-New Guinea, People's Republic of China, Peru, the Philippines, Russia, Singapore, South Korea, Thailand, United States, and Vietnam.

[133] *See* INTERNATIONAL CONFERENCE ON HARMONISATION, *ICH Steering Committee Embarks on Phase Two Harmonisation*, PRESS REPORT, Feb. 1998 (*available at* <http://www.pharmweb.net/pwmirror/pw9/ifpma/ich7.html>).

quate attention to the GMP controls applied to ingredients, in the country of origin, is essential to the safety and quality of these substances. Current safeguards used by FDA and other regulations — e.g., finished dosage form manufacturers' checks of ingredients, inspections of manufacturers of key ingredients in products with proposed approvals pending, application to bulk drug manufacturers of those general GMP requirements that are relevant, and controls over the substances themselves through such measures as an ICH guideline on drug impurities[134] — are helpful but do not meet the need for a comprehensive approach. Particularly considering the fact that bulk pharmaceutical chemicals are increasingly manufactured in developing countries such as China and India, a new ICH initiative to draft harmonized GMPs applicable to APIs, for adoption and enforcement in all countries that produce such chemicals, is critically important.[135]

G. Harmonization: Medical Device Regulation

Many of FDA's medical device harmonization activities are carried out through a group known as the Global Harmonization Task Force (GHTF).[136] The GHTF is FDA's highest priority for international device activities. Work on standards through the International Standards Organization and other groups also remains vitally important. The GHTF is an informal grouping that includes government and industry officials from Europe, North America, and Asia-Pacific. Principal government participants are from the European Commission and the fifteen countries of the EU, the United States, Canada, Japan, and Australia. The GHTF has four work groups known as study groups, dealing with product approval-related issues, adverse event reporting, GMPs (now called quality systems requirements), and audits of quality systems.

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[134] *See infra* note 135.

[135] In early 1998, the participants in ICH decided to develop an ICH guideline on APIs, an activity that may in the future be extended to inactive ingredients, such as excipients, as well. This activity will be done in conjunction with PIC/S and WHO, and began with a joint meeting in April, 1998. Thus, existing activities are likely to be folded into a group that will be treated as comprising at least PIC/S, WHO, and ICH, and focused initially on APIs. A GMP on inactive ingredient GMPs remains a future possibility.

[136] *See* Horton, *FDLI Device Harmonization*, *supra* note 2, at 587-88.

III.

A. *FDA Policy on Agreements with Regulatory Counterparts in Other Countries*

FDA has expressed support for agreements with other countries to enhance public health protection and facilitate commerce in safe and quality food, drugs, and medical devices consistent with public health protection and the requirements of the law, through a 1995 policy document on initiating, developing, and monitoring MOUs that was set forth in a Compliance Policy Guide (Guide):

> It is the policy of FDA to pursue the development of MOU's that will further the agency's public health mission [and are] designed to meet the following goals:
>
> (1) To enhance FDA's ability to ensure that regulated products are safe, effective, of good quality, and properly labeled;
>
> (2) To allow FDA to utilize its resources more effectively or efficiently, without compromising its ability to carry out its responsibilities; and
>
> (3) To improve communications between FDA and foreign officials concerning FDA regulated products.[137]

The Guide described three long-standing categories of FDA MOUs as examples: (1) reciprocal agreements with countries having the same or similar systems, (2) agreements dealing with certification of imports or exports, and (3) agreements to formalize communication and cooperation in the interest of harmonization, improved FDA decision-making, and reduced expenditures on import control.[138]

A variety of MOUs is possible: (1) A cooperation MOU, exemplified by an agreement signed by FDA and its counterparts in Canada and Mexico (Memorandum of Cooperation in FDA International Cooperative Agreements Manual), contemplates mutual cooperation and information-sharing activities; (2) A compliance MOU, which may be reciprocal or one-way, contemplates compliance by the exporting country with the requirements of the importing country; (3) An equivalence MOU contemplates a finding that the other country has a regulatory system equivalent to FDA's; as discussed above, notice-and-comment requirements may come into play when FDA

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[137] 60 Fed. Reg. 31,485 (1995).

[138] *See id.*

makes a determination that another country's regulatory food system is equivalent.

FDA insists upon equivalence as a prerequisite to mutual recognition. Therefore, in FDA's usage, MRAs might be viewed as a high order of agreement, a reciprocal agreement reached after a finding that the MOU partner's system is sufficiently trustworthy that FDA can safely reduce coverage of the product from the other country. A few long-standing FDA MOUs contain mutual recognition features, including several agreements on good laboratory practices. Also, for more than a quarter century FDA has had MOUs with regulatory counterparts in Canada[139] and Sweden[140] that include mutual acceptance of results from inspections for compliance with GMPs. Likewise, FDA and its counterparts in Australia and the U.K. have similar agreements under which reports are exchanged on device GMP inspections.[141]

Not all agreements are reciprocal, nor need they be to offer benefits to both sides. An example are the MOUs reached between FDA and its Russian counterparts.[142] Although the MOUs address regulatory cooperation and are not reciprocal in that they facilitate the marketing in Russia of FDA-approved drugs without corresponding provisions on marketing in the United States of drugs approved by Russian authorities, they benefited Russia by assisting in the prompt access to high-quality U.S. products at a time of medical product shortages. Further, they helped Russia by facilitating increased emphasis by Russian authorities on more problematic products entering Russia from other parts of the world.

FDA has more than fifty agreements with its counterparts in other countries. The Agency publishes these agreements in the Federal Register[143] and periodically publishes a compilation of them.[144] These agreements generally are called "memoranda of understanding" (MOUs) or, if needed by the foreign counterpart,

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[139] *See* FDA, *Agreement of Cooperation Between the Canadian Department of National Health and Welfare and the Food and Drug Administration*, Sept. 28, 1973, *in* INTERNATIONAL COOPERATIVE AGREEMENTS MANUAL 39-41 (Nov. 1996) [hereinafter FDA, *Canadian Agreement*]. (The Canadian Department of National Health and Welfare is now called Health Canada).

[140] *See* FDA, *Memorandum of Agreement Between the Swedish National Board of Health and the Food and Drug Administration*, Oct. 17, 1972, *in* INTERNATIONAL COOPERATIVE AGREEMENTS MANUAL 337-39 (Nov. 1996).

[141] *See id.* at 17-20, 353-56.

[142] *See id.* at 287, 295, 325.

[143] *See* 21 C.F.R. §§ 10.90(d), 20.108 (1998).

[144] *See* FDA, INTERNATIONAL COOPERATIVE AGREEMENTS MANUAL 59-62 (Nov. 1996).

"arrangements" or "memoranda of cooperation" (MOCs). As has been discussed, some of these agreements are closely related to "mutual recognition features" in that they call for exchange of inspection results.

The equivalence provisions in the World Trade Organization Agreement on the Application of Sanitary and Phytosanitary Measures have spawned numerous efforts to define what should enter into countries' findings that others' food safety systems are equivalent. In 1997, FDA published in the Federal Register a proposed guidance document concerning its determinations of equivalence of other countries' food control systems.[145] The final guidance, to be issued by FDA in the future, will be useful in FDA's determination of food system equivalence generally, including implementation of FDA's 1995 seafood regulation.[146] This regulation includes provisions on imported seafood that have the effect of streamlining the requirements on importers if they purchase seafood from countries whose regulatory bodies have equivalence agreements or compliance agreements with FDA.[147] In 1998, the expectation was that FDA would begin to propose determinations of equivalence of other countries' seafood systems, possibly starting with Canada. Because of the requirement that FDA employ a notice-and-comment process in its food safety equivalence determinations — as a result of the 1994 Uruguay Round Agreements Act[148] discussed above — FDA is expected to undertake a notice-and-comment process with respect to each equivalence determination entered into under this regulation. A country that has agreed to commit that its exports to the United States will comply with FDA requirements would not require a notice-and-comment process, as discussed elsewhere in this Article.

A draft guideline that the Agency is helping to shepherd through the United Nations Food Standards Programme, known as the Codex Alimentarius Commission, is useful in articulating "equivalence." In the Codex Committee on Import, Export, Food Inspection and Certification Systems, FDA was the rapporteur for "Proposed Draft Guidelines for the Development of Equivalence

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[145] *See* 62 Fed. Reg. 30,593 (1997).

[146] *See* 21 C.F.R. pt. 123 (1998).

[147] *See* 21 C.F.R. § 123.12 (1998). In a compliance agreement, each side pledges that its exporting processors will meet the requirements of the importing country.

[148] *See* 19 U.S.C. § 2578a (1994). FDA is singled out in this statute because use of a notice-and-comment rulemaking process was already the practice of the Food Safety Inspection Service of USDA. See, for example, the addition of Mexico to the list of countries eligible to export poultry products into the United States. *See* 62 Fed. Reg. 63,284 (1997).

Agreements Regarding Food Import and Export Inspection and Certification Systems" that may be adopted as Codex Guidelines as early as 1999.[149] Also, FDA and United States Department of Agriculture officials are contributing to the development of a related document that discusses issues concerning the judgment of equivalence.[150]

B. Harmonization: Equivalence or Mutual Recognition?

As may be evident, the term MRA has become popular among those involved in regulations, trade, standards, and conformity assessment discussions. Yet those who use the term do not always use it in the same way. A fundamental question is always: whose requirements are being met?

Is it the "customer's" requirements that are being met, i.e., the importing country? Private testing bodies such as Underwriters Laboratories, for example, test to the requirements of the customer. The international analogue is that the conformity assessment be done in accordance with the laws of the importing country. Or, conversely, is it the supplier's requirements that are being met, i.e., those of the exporting country's? There is a widespread desire in industry to be able to export if the requirements of the exporting country have been met. For example, a United States-EU industry meeting known as the Transatlantic Business Dialogue has espoused the concept of "tested once, accepted everywhere."

From an FDA standpoint, there must be considerable harmonization for the Agency to enter an agreement that relies upon another country's system of GMPs or other aspects of product conformity. There is also the possibility of an uneven playing field to the disadvantage of domestic producers if they continue to be held to stricter domestic requirements while foreign competitors operate in countries whose laws and enforcement are laxer yet whose products could enter the U.S. market based solely on compliance with the laws of the foreign competitor. Clearly, equivalence contemplates more than laws that, on paper alone, provide an equivalent level of protection. Unless equivalence is achieved in the application and enforcement of written legal requirements, an uneven playing field may develop. Under FDA law and policy, an MRA contemplates a finding that the

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[149] Joint FAO/WHO Food Standards Programme, *Report of the Sixth Session of the Codex Committee on Food Import and Export Inspection and Certification Systems,* Codex Alimentarius Commission, 6th Sess., App. II, at 37, ALINORM 99/30 (1998).

[150] *See id.*, Agenda Item 8, at ¶ 41-52 (paper prepared by New Zealand with assistance from Australia, Canada, and the United States, CX/FICS 98/7).

other country has an equivalent regulatory system to FDA's in its application as well as its wording.

C. U.S.-EU MRA

From 1994 to 1998, FDA's principal focus of activity in the area of agreements with other countries concerning drugs and devices has entailed negotiations with the European Commission, aimed at mutual reliance on one another's inspections. An MRA between the U.S. government and the European Commission (EU MRA) with annexes on drugs and devices was initialed by the two sides on June 20, 1997, signed on May 18, 1998, and is now in the early stages of implementation, beginning with a three-year transitional phase inaugurated by an exchange of letters on October 30, 1998.[151] A summary of the EU MRA is provided in an Appendix to this Article.

The discussions that led to the EU agreement were part of broad negotiations on a mutual recognition agreement led by the Office of the United States Trade Representative. These negotiations included not only drug GMPs and medical devices, but also telecommunications, electrical safety, and recreational craft GMPs. The European Commission's insistence on a "balanced package" meant that it would not agree to MRAs on telecommunications and recreational craft — viewed as advantageous to the United States — unless there also was MRA coverage of pharmaceuticals — viewed as advantageous to the EU. (More pharmaceuticals are exported to the United States from the EU than are imported.)

The European Commission's goal in seeking MRAs was to facilitate the marketing in other countries of drugs and devices produced in the EU, through the reduction of both foreign inspections for drugs and devices and border batch testing for drugs. Also, for medical devices the European Commission hoped that FDA could delegate to EU conformity assessment bodies the task of assuring that all FDA requirements had been satisfied. The latter objective was inconsistent with FDA's authority and policies, so the agreement reached was more modest in its purpose and effect.

Regarding both drugs and devices, the EU MRA provides for the exchange of inspection reports on compliance with GMPs. The agreement was facilitated by the fact that the United States and the EU have already harmonized major parts of the GMP requirements for both categories of products. As noted earlier, the EU still needs

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[151] AGREEMENT ON MUTUAL RECOGNITION BETWEEN THE UNITED STATES OF AMERICA AND THE EUROPEAN COMMUNITY, June 20, 1997 (available at <http://www.ustr.gov>).

to enact GMP requirements for active pharmaceutical ingredients. Furthermore, considerable confidence-building work, and probably harmonization activities, will be needed on the conduct of inspections and on what follow-up action is taken in cases of nonconformity.

D. Rulemaking on the MRA

FDA published a notice of proposed rulemaking in the Federal Register inviting comments on the MRA and its implementation, as well as a final rule. [152] Comments were received from domestic and foreign manufacturers and consumer organizations. Of course, the Agency will evaluate potential enhancements as EU and FDA policies evolve. The agreement thus provides a solid ongoing basis for further joint work.

E. Effect of FDAMA on the Device MRA

Due to FDAMA, FDA will need to seek changes in the lists of devices eligible for the pre-market assessment provisions that are appended to the sectoral annex on medical devices. This is because FDAMA eliminated the 510(k) pre-market notification requirement for most Class I devices and certain Class II devices.[153] These exemptions will eliminate the need for these devices to be subjected to the pre-market notification assessment provisions of the MRA, although the devices remain subject to the quality system GMP aspects of the MRA. FDAMA also provides for expansion of the third-party approach to many more Class II devices, once guidance documents are written for third-party reviews. At the same time, four devices needed to be deleted from the MRA, due to provisions in FDAMA that disallowed use of third parties to review permanently implantable devices or life sustaining devices.[154]

The MRA builds upon the fact that FDA had conducted a pilot program of third-party review by private sector bodies of pre-market notifications (510(k)s) for certain devices. FDAMA codified this pilot program. This new law includes provisions consistent with the MRA in two respects: FDA needs to "accredit" conformity assessment bodies (rather than relying upon accreditations by the EU countries or

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[152] *See* 63 Fed. Reg. 17,744 (1998). See *supra* note 86 for additional notices relevant to the sectoral annex on medical devices.

[153] *See* 63 Fed. Reg. 3,142 (1998); 63 Fed. Reg. 5,387 (1998).

[154] *See* FFDCA § 523; 21 U.S.C.A. § 360m (West Supp. 1998).

other MRA partners), and FDA needs to make the final decisions on product approvals.[155]

F. Agreements with Other Countries: Plan on Recognition of GMP Inspections

Because of FDA resources involved in implementing the confidence-building and equivalence-determination aspects of the EU MRA, finding time for similar activities with other countries will be difficult. One approach under consideration is a straightforward agreement to cooperate and exchange inspection reports, without efforts by either side to limit the ability of the other to perform inspections, to require additional information from firms, or to make whatever use of an inspection report the regulator receiving it sees fit. An agreement of this type with Australia's Therapeutic Goods Administration is under review in FDA.

In recent years, FDA and its counterparts in Canada and Switzerland[156] initiated discussions relating to an updated drug GMP agreement, which would modernize MOUs with those countries that have aided international cooperation for more than a quarter of a century.[157] FDA is likely to resume these activities in coming years.

On May 20, 1998, as required by FDAMA,[158] FDA made public a "plan that establishes a framework for achieving mutual recognition of good manufacturing practices inspections."[159] This plan highlighted both the desirability of agreements with other countries and the practical impediments that stand in the way. Explaining that "FDA's limited resources force the Agency to focus on certain high priorities in these general areas which are likely to have the most significant impact on protecting the domestic public health,"[160] the plan described the Agency's current priority areas to include:

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[155] *See id.*

[156] *See* Agreed Minutes of Meeting between FDA officials and Swiss officials (July 9, 1998) (on file with the *Seton Hall Law Review*).

[157] *See* Letter from Dean Rusk, Secretary of State, dated Oct. 28, 1968, in response to letter from Felix Schnyder, Ambassador of Switzerland, dated June 28, 1968, (on file with FDA, INTERNATIONAL COOPERATIVE AGREEMENTS MANUAL 341-42 (Nov. 1996)); *see also* FDA, *Canadian Agreement*, *supra* note 139.

[158] 21 U.S.C.A. § 383(c)(4) (West Supp. 1998).

[159] *FDA Homepage* (visited Nov. 2, 1998) <http://www.fda.gov/oc/fdama/fdamagmp.html> (to view this plan).

[160] *Id.*

- Implementing the EU MRA;
- Completing harmonization projects essential to the future success of that MRA, e.g., GMPs for APIs and inspectional guides for device GMP inspections;
- Strengthening long-standing arrangements on exchange of inspection information with other countries; and
- Seeking opportunities for low-cost arrangements for information exchange.[161]

Therefore, under the latter two elements of the Agency's priorities, continued efforts will be made to strengthen existing agreements with Switzerland and Canada, and unilateral or reciprocal arrangements, such as access to one another's databases on compliance status, may be undertaken.

IV. CONCLUSION

FDA's activities on harmonization and agreements with other countries are both promising and complex, raising a host of legal and policy issues for the Agency, other parts of the U.S. governments and foreign counterparts. These initiatives are an important part of FDA's vision for the next century, as the Agency expects to rely on the efforts of equivalent foreign authorities as partners in consumer protection.

V. APPENDIX

Summary of the MRA with the EU on Drugs and Devices[162]

The EU MRA includes two sectoral annexes covering pharmaceuticals and medical devices, products regulated by FDA. The pharmaceutical annex covers post- and pre-approval good manufacturing practice inspections, and the medical device annex covers quality system audits and pre-market evaluation reports of certain medical devices. The annexes describe systems under which the participating parties, regulatory authorities, and CABs will exchange information concerning the products and processes subject to the annexes. The annexes also describe how the participating parties will

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[161] *See id.*

[162] *See Summary of the FDA-Related Elements of the "Agreement on Mutual Recognition Between the United States of America and the European Community"* (visited Nov. 2, 1998) <http://www.fda.gov/oia/mrasum.htm> (FDA posted this document as a companion to its April 10, 1998 proposed rule (63 Fed. Reg. 17,744 (1998))). The entire Appendix relies heavily upon this summary. The author is indebted to work done by Anne Miller, Office of the Chief Counsel, FDA, on this summary.

regard information they receive pursuant to the annexes. Neither annex changes current FDA regulation of these product areas.

The EU MRA also includes an "umbrella agreement," which describes a system for the efficient functioning of the MRA's annexes. Several provisions in the umbrella agreement will not apply to FDA's activities under its sectoral annexes. For example, umbrella provisions concerning CABs do not apply to the pharmaceutical annexes, because these annexes do not utilize CABs. In addition, because the medical device annex includes its own, specific provisions governing CABs, the umbrella provisions regarding CABs will not usually apply. Article 22.2 of the umbrella agreement provides that when there is an inconsistency between the annexes and the umbrella, provisions in the sectoral annexes will apply in the first instance.

The umbrella includes a number of provisions, however, that can affect FDA's operation under its sectoral annexes. Examples of such provisions include the provision establishing the Joint Sectoral Committee (Article 14 of the umbrella agreement) and the provision regarding confidentiality (Article 17 of the umbrella agreement).

Pharmaceutical GMP Annex

The stated purpose of the pharmaceutical GMP annex is to "govern the exchange . . . and normal endorsement . . . of official Good Manufacturing Practices (GMP) inspection reports after a transitional period aimed at determination of the equivalence of the regulatory systems of the Parties . . . ." To this end, the annex describes activities and processes that will occur during two distinct periods, the transitional period and the operational period, which will lead to exchange and possible normal endorsement of pharmaceutical GMP inspection reports. The annex applies to certain types of pharmaceutical products, which are described in the annex. An indicative list of products subject to the annex appears in Appendix 3 of the annex.

Immediately after the effective date of the EU MRA, FDA and the appropriate regulatory authorities in the EU will begin a three-year transition period. During this period FDA will participate in confidence-building activities with its counterpart pharmaceutical regulatory authorities in the EU. Such activities will include information exchange, joint training, and joint inspections. The purpose of the activities will be to enable FDA eventually to assess equivalence of its counterpart regulatory authorities in the EU and to enable these authorities eventually to assess equivalence of FDA. FDA and EU

regulatory authorities will assess equivalence according to certain criteria, which are found in Appendix 4 of the annex.

According to Article 1.1 of the annex, "equivalence" means that the "regulatory systems are sufficiently comparable to assure that the process of inspection and the ensuing inspection reports will provide adequate information to determine whether respective statutory and regulatory requirements of the authorities have been fulfilled." Equivalence does not, however, require that the systems have "identical procedures."

At the end of the three-year transition period, FDA will make equivalence determinations of each EU regulatory authority that participated in the confidence-building activities. The EU regulatory authorities which participated in the confidence-building activities will, likewise, make an equivalence determination of FDA. The determinations will be based on the body of evidence assessed during the transition period, and determinations of equivalence will be made upon a showing of "a demonstrated pattern of consistent performance" in accordance with the criteria in Appendix 4.

To monitor activities performed under this annex, the parties will establish a "Joint Sectoral Committee" (Committee), which will be co-chaired by a representative of FDA and a representative from the EU. Each representative will vote on each matter before the Committee, and decisions in the Committee will be taken by unanimous consent. The Committee's functions include, among other things, making a joint assessment of equivalence of the authorities at the end of the transition period. After the joint assessment, the Committee will create a list of authorities determined to be equivalent, based on FDA determination as to EU authorities and EU determination as to FDA. Authorities not listed as equivalent at that time may apply for reconsideration at a later date.

After equivalence determinations have been completed, the operational period will begin. During this period, equivalent authorities may exchange pharmaceutical GMP inspection reports. Post-approval GMP inspection reports for products covered under this annex will be transmitted to the regulatory authority requesting such a report within sixty calendar days of the request. In some instances, the regulatory authority receiving a request may not possess a current GMP inspection report for the particular manufacturing establishment that is the subject of the request. In this situation, a "new" inspection must be performed, and the resulting inspection report will be transmitted to the requesting authority within ninety calendar days from the request.

For transmission of pre-approval GMP inspection reports, equivalent regulatory authorities will give preliminary notification that an inspection may need to take place. Within fifteen calendar days of the notification, the regulatory authority requested to perform an inspection will acknowledge receipt of the notice and will confirm its ability to perform the inspection. If the authority performs such inspection, the resulting report will be sent to the requesting authority within forty-five calendar days of the request. The request must, however, include appropriate information and the precise issues to be addressed during the inspection. If, in an exceptional case, an authority requests a report to be transmitted in a shorter time, it must describe the exceptional circumstances in the request. If a regulatory authority is unable to perform the inspection as requested, the authority making the request will have the right to conduct the inspection itself.

Once an equivalent authority receives an inspection report from another equivalent authority (post- or pre-approval reports), the receiving authority will "normally endorse" the report. Normal endorsement will be based on findings in the report as they are measured against the importing country's own laws. In other words, FDA may normally endorse an inspection report from an equivalent EU authority based on what the report says about compliance with U.S. GMP laws and regulations. Normal endorsement will occur "except under specific and delineated circumstances," and will be "based on the determination of equivalence in light of the experience gained." (See Article 12 of the annex.) The effect of this language is not only to allow a receiving authority to accept findings stated in a report transmitted by another equivalent authority, but also to allow a receiving authority to make final determinations of GMP compliance. Thus, assuming it is found to be equivalent, FDA will retain the ability to make final determinations as to compliance with U.S. GMP laws and regulations. FDA expects, however, that it will be able to accept most findings in the inspection reports it receives from equivalent authorities.

The pharmaceutical annex contains several other provisions that govern its operation. For example, equivalent authorities will participate in activities to monitor equivalence, including review of inspection reports, a limited number of joint inspections, and common training sessions. In addition, during the transitional period, the authorities will develop an alert system, and means of exchanging information on confirmed problem reports, corrective actions, recalls, rejected import consignments, and other regulatory and enforce-

ment problems for products subject to this annex. In addition, during the operational period, each party has the right to request suspension of an equivalent authority.

Finally, a crucial provision affirming the regulatory authorities' role in protecting the public health recognizes that regulatory authorities may fulfill their "legal responsibilities by taking actions necessary to ensure the protection of human and animal health." The authorities may take such actions in accordance with the level of protection they consider appropriate. (See Article 21 of the annex.)

Medical Device Annex[163]

The medical device annex's stated purpose is "to specify the conditions under which a Party will accept the results of quality system-related evaluations and inspections and pre-market evaluations of the other Party . . . as conducted by listed conformity assessment bodies (CABs) and to provide for other related cooperative activities." The annex applies to exchange and possible endorsement of certain types of reports from equivalent CABs, including surveillance/post-market and initial/pre-approval inspection reports, premarket (510(k)) product evaluation reports, quality system evaluation reports (as referred to in the EU), and examination and verification reports (as referred to in the EU).

Similar to the pharmaceutical GMP annex, the medical device annex is based on the concept of equivalence. Under the medical device annex, equivalence means the following: CABs in the EU are capable of conducting product and quality systems evaluations against U.S. regulatory requirements in a manner equivalent to those conducted by FDA; and CABs in the United States are capable of conducting product and quality systems evaluations against EU regulatory requirements in a manner equivalent to those conducted by EU CABs.[164]

The concept of equivalence will apply to the three distinct components of the medical device annex, each covering a discrete range of products. The three components are: quality system evaluations, which will be exchanged with regard to all products regulated as medical devices under both U.S. and EU law; product evaluation reports, which will be exchanged only with regard to those products classified under the U.S. system as Class I and Class II-Tier 2 medical

[163] For additional guidance, *see* 63 Fed. Reg. 28,392 (1998); 63 Fed. Reg. 36,240 (1998).

[164] *See* 63 Fed. Reg. 36,240 (1998).

devices (listed in Appendix 2 of the annex); and post-market vigilance reports, which will be exchanged with regard to all products regulated as medical devices under both U.S. and EU law.

The medical device annex, like the pharmaceutical GMP annex, includes a three-year transitional period, which will begin immediately after entry into force of the EU MRA. During this period, parties will participate in confidence-building activities in an effort to obtain a sufficient body of evidence to make equivalence determinations of CABs. Such activities include seminars and workshops, exchange of information, joint training exercises, and observed inspections. The parties will designate CABs to participate in these activities by transmitting a list of CABs that meet technical competence and independence criteria, which are found in Appendix 1 of the medical device annex. During the transition period, the parties also will jointly determine the information that must be present in quality system and product evaluation reports, and they will jointly develop a notification and alert system, which will be used in cases of defects, recalls, and other problems.

During the last six months of the transition period, the parties will make a joint assessment of equivalent CABs that participated in the confidence-building activities. CABs found to be equivalent will have demonstrated proficiency by submitting a sufficient number of adequate reports. Equivalence assessment of a particular CAB may be limited in scope; a list of equivalent CABs and a full explanation of the scope of their equivalence eventually will be found in Appendix 5 of the medical devices annex. Decisions concerning CAB equivalence must be agreed to by both parties. CABs not listed for participation in confidence building activities, or listed for certain types of evaluations, may apply for participation at a later date once necessary measures have been taken or sufficient experience has been gained.

After the transition period and the establishment of a list of equivalent CABs, the parties will begin the operational period, and the operational period will apply only to those CABs found to be equivalent. The parties will exchange information on quality system evaluation reports and product evaluation reports. Exchange of quality system evaluation reports during the operational period will proceed as follows:

- European CABs listed as equivalent will provide FDA with full quality system evaluation reports for pre-approval quality system evaluations;
- European CABs listed as equivalent will provide FDA with abbreviated surveillance quality system evaluation reports;
- U.S. CABs listed as equivalent will provide the EU Notified Body (chosen by the manufacturer) full reports of initial quality system evaluations and abbreviated reports of quality system surveillance audits.

When a CAB listed as equivalent receives a request for a quality system evaluation report, it will transmit the report within sixty calendar days of the request. In the event that a party requests a new inspection (e.g., when there is not a current quality system evaluation report), the CAB will have an extra thirty calendar days to transmit the report to the requesting party. If an inspection cannot be performed within the specified period of time, the requesting party may perform the inspection on its own.

Similar to the GMP reports exchanged under the pharmaceutical annex, quality system evaluation reports prepared by listed CABs and exchanged under the medical device annex will normally be endorsed by the party receiving the information. The party will normally endorse such reports except under specific and delineated circumstances, and based on the determination of equivalence in light of the experience gained.

Exchange of product evaluation reports will proceed as follows:

- EU CABs found equivalent for the purpose of exchanging such reports will provide FDA with 510(k) pre-market notification assessment reports, prepared to U.S. medical device requirements;
- U.S. CABs, subject to the specifications and limitations on the list of equivalent CABs, will provide to the EU Notified Body (chosen by the manufacturer) type examination and verification reports prepared to EU medical device requirements.

Transmission of these product evaluation reports will take place according to the receiving party's specified procedures. Product evaluation reports prepared by listed CABs and exchanged under this annex will normally be endorsed by the party receiving the reports, except under specific and delineated circumstances, and based on the determination of the CABs's equivalence in light of the experience gained. Additional activities under this annex include monitoring CABs listed as equivalent, listing of additional CABs during the operational phase, continued participation in activities of the GHTF

for medical devices, establishing an alert system and contact points, and establishing a Joint Sectoral Committee.

Under an MOU between FDA and the Office of the United States Trade Representative, FDA speaks for the government on discussions relating to FDA's regulatory responsibilities and authority, in both the Joint Committee under the umbrella agreement and in the Joint Sectoral Committees for drugs and devices.