DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 94D–0300]

International Harmonization; Policy on Standards

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the agency's policy on the development and use of standards with respect to international harmonization of regulatory requirements and guidelines. Specifically, the policy is intended to address the conditions under which FDA plans to participate with standards bodies outside of FDA, domestic or international, in the development of standards applicable to products regulated by FDA. The policy also covers the conditions under which FDA intends to use the resultant standards, or other available domestic or international standards, in fulfilling its statutory mandates for safeguarding the public health.

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SUPPLEMENTARY INFORMATION: In a notice published in the **Federal Register** of November 28, 1994 (59 FR 60870), FDA published a draft policy on international harmonization of regulatory requirements and guidelines. The purpose of the draft policy was to articulate FDA's policy on the development and use of standards with respect to international harmonization of regulatory requirements and guidelines. The agency gave interested persons an opportunity to comment on the draft policy document. A discussion of the comments received and the agency's responses is found in section III. of this document.

Background information as well as the text of the policy follow:

International Harmonization of Regulatory Requirements and Guidelines

I. Background

The purpose of this document is to articulate FDA's policy on development and use of standards with respect to international harmonization of regulatory requirements and guidelines. As used throughout this document, the term ''standards'' includes what are commonly referred to as ''consensus standards,'' ''voluntary standards,'' and ''industry standards.'' Also, FDA sometimes accepts standards and makes them mandatory regulatory requirements. Although the draft policy focuses on international harmonization and international standards, its principles are applicable as well to domestic standards activities in which FDA participates.

A. Statutory Mandates for FDA-Regulated Products

FDA is the principal regulatory agency within the Public Health Service (PHS). The agency protects the public health by, among other things, implementing statutory provisions designed to ensure that food is safe and otherwise not adulterated or misbranded; that human and veterinary drugs, human biological products, and medical devices are safe and effective; that cosmetics are safe; and that electronic product radiation is properly controlled. FDA-regulated products must be truthfully and accurately labeled and in compliance with all applicable laws and regulations. The statutory mandates for safeguarding the public health in these product sectors are prescribed in several statutes, notably in the Federal Food, Drug, and Cosmetic Act; the Public Health Service Act; and the Fair Packaging and Labeling Act.

B. International Harmonization of Regulatory Requirements and Guidelines

In recent decades, great changes in the world economy, together with expanded working relationships of regulatory agencies around the globe, have resulted in increased interest in international harmonization of regulatory requirements. Increased international commerce, opportunities to enhance public health through cooperative endeavors, and scarcity of government resources for regulation have resulted in efforts by the regulatory agencies of different nations to work together on standards and harmonize their regulatory requirements. Such harmonization enhances public health protection and improves government efficiencies by reducing both unwarranted contradictory regulatory requirements and redundant applications of similar requirements by multiple regulatory bodies. Harmonization facilitates cooperation in regulatory activities.

Harmonization of FDA's regulatory requirements and guidelines with those of other countries was recently embraced as a pillar of the President's and Vice President's National Performance Review. In *Reinventing Drug and Device Regulation* (April 1995), international harmonization was identified as a high priority initiative across FDA programs. Recognizing the considerable synergy between its domestic policy and its international policy priorities, FDA is sharpening and focusing its planning for enhanced alignment of FDA and international standards.

In 1992, an FDA Task Force on International Harmonization had provided a broad assessment of the goals, scope, and direction of FDA's international activities. These activities were found to comprise a wide variety of efforts by FDA to retain and strengthen its public health safeguards, while striving toward common ground with its foreign government counterparts on product standards, criteria for the assessment of test data, and enforcement procedures. The task force's recommendations for the agency included an overall FDA policy on international harmonization, which is to encourage the initiation and support of efforts, consistent with the agency's goals and principles, that will further the international harmonization of standards and policies for the regulation of products for which FDA has authority. Soon thereafter, FDA's strategic plan began to recognize standards as the premier focus of the agency's international activities.

1. Goals

FDA's goals in participating in international harmonization are:

- To safeguard U.S. public health,
- To assure that consumer protection standards and requirements are met,
- To facilitate the availability of safe and effective products,
- To develop and utilize product standards and other requirements more effectively, and
- To minimize or eliminate inconsistent standards internationally.

2. General Principles

FDA participation in international harmonization efforts should be guided by the following general principles:

- The harmonization activity should be consistent with U.S. Government policies and procedures and should promote U.S. interests with foreign countries.
- The harmonization activity should further FDA's mission to protect the public health by, among other things, ensuring that food is safe and otherwise not adulterated or misbranded; that human and veterinary drugs, human biological products, and medical devices are safe and effective as required by law and are not adulterated or misbranded; that cosmetics are not adulterated or misbranded; that electronic product radiation is properly controlled; and that all of these products are labeled truthfully and informatively.
- FDA's input into international standard setting activities should be open to public scrutiny and should provide the opportunity for the consideration of views of all parties concerned.
- FDA should accept, where legally permissible, the equivalent standards, compliance activities, and enforcement programs of other countries, provided that FDA is satisfied such standards, activities, and programs meet FDA's level of public health protection.
- Scientific and regulatory information and knowledge should be exchanged with foreign government officials, to the extent possible within legal constraints, to expedite the approval of products and protect public health.

Thus, the agency's primary goal in all of its international harmonization activities is to preserve and enhance its ability to accomplish its public health mission. Global harmonization is also approached with the aim of enhancing regulatory effectiveness, by providing more consumer protection with scarce government resources, and increasing worldwide consumer access to safe, effective, and high quality products.

C. Other Obligations and Policies

1. International Agreements

The U.S. Government is a party to international trade agreements. In the United States, such trade agreements become effective only after implementing legislation is signed into law. FDA has participated in recent international trade negotiations to ensure that FDA's requirements are preserved and that regulatory practices can remain focused on fulfilling the agency's mission to protect the public health while being supportive of emerging, broader U.S. Government obligations and policies. In addition, FDA continues to be involved in work of the World Trade Organization (WTO) as well as the North American Free Trade Agreement (NAFTA) committees on sanitary and phytosanitary measures, and on technical barriers to trade, in order to foster international harmonization of regulatory requirements and to facilitate consultation on trade issues. Recently FDA has begun to be involved in other regional activities, e.g., the Forum on Asia Pacific Economic Cooperation (APEC), work on initial steps toward a Free Trade Area of the Americas (FTAA), and work towards a Transatlantic Area that strengthens our ties with Europe.

The principal international trade agreement is the General Agreement on Tariffs and Trade (GATT), which entered into force on January 1, 1948. GATT has since been amended several times following negotiation sessions known as rounds.

The GATT Agreement on Technical Barriers to Trade (TBT), popularly known as the Standards Code, was negotiated during the Tokyo Round of the GATT in the 1970's and entered into force on January 1, 1980. As part of a general effort to reduce unnecessary nontariff barriers to trade, the TBT agreement was intended to promote use by countries of standards, technical regulations, and conformity assessment procedures that are based on work done by international standards bodies. The implementing legislation for the TBT agreement, provided in the Trade Agreements Act of 1979 as amended in 1994 (Pub. L. 103–465; 19 U.S.C 2531–2582), has thus provided additional authority for FDA's international standards activity. To assure that harmonization does not result in lowering safety or quality standards for U.S. consumers, this law contains the safeguard that:

''* * * No standard-related activity of any private person, Federal agency, or State agency shall be deemed to constitute an unnecessary obstacle to the foreign commerce of the United States if the demonstrable purpose of the standards-related activity is to achieve a legitimate domestic objective including, but not limited to, the protection of legitimate health or safety, essential security, environmental, or consumer interests and if such activity does not operate to exclude imported products which fully meet the objectives of such activity.''

The most recent GATT round, the Uruguay Round, was concluded on December 15, 1993, and was formally signed at the Marrakech Ministerial Meeting on April 15, 1994. The new WTO will administer the new GATT and other Uruguay Round agreements, and every country that is a member of the WTO will be required to adhere to all of these agreements. On December 8, 1994, Pub. L. 103–465 was enacted in the United States to approve and implement the Uruguay Round agreements. This law included updating changes in the Trade Agreements Act that reaffirmed the duty of Federal agencies to participate in international standards activities, subject to available resources.

One of the agreements of the Uruguay Round administered by the WTO is the new agreement on TBT, which is similar in many respects to the 1980 TBT agreement. As with the 1980 TBT agreement, the purpose of the new TBT agreement is to ensure that product standards, technical regulations, and related procedures do not create unnecessary obstacles to trade. The new TBT agreement ensures, and clearly states, that each country has the right to establish and maintain technical regulations for the protection of human, animal, and plant life and health and the environment, and for prevention against deceptive practices.

In the new TBT agreement, the term ''standard'' is defined as:

''[A] document approved by a recognized body, that provides, for common and repeated use, rules, guidelines or characteristics for products or related processes and production methods, *with which compliance is not mandatory* [emphasis added]. It may also include or deal exclusively with terminology, symbols, packaging, marking or labelling requirements as they apply to a product, process or production method.''

Also, ''technical regulation'' is defined as:

''[A] document which lays down product characteristics or their related processes and production methods, including applicable administrative provisions, *with which compliance is mandatory* [emphasis added]. It may also include or deal exclusively with terminology, symbols, packaging, marking, or labelling requirements as they apply to a product, process or production method.''

Thus, in the language of the new TBT agreement, when a government acts to accept a voluntary standard to make it mandatory, the resulting document is a technical regulation. A measure used to ascertain compliance with a standard or technical regulation is a conformity assessment procedure.

The new TBT agreement continues and strengthens the reference to international standards found in the 1980 TBT agreement. Specifically, the agreement states that, where technical regulations are required and relevant international standards exist or their completion is imminent, WTO-member countries shall use them, or the relevant parts of them, as a basis for their technical regulations, except when such international standards or relevant parts would be an ineffective or inappropriate means for the fulfillment of the legitimate objectives pursued. Further, the agreement states that, with a view towards harmonizing technical regulations on as wide a basis as possible, WTO-member countries shall play a full part within the limits of their resources in the preparation by appropriate international standards bodies of international standards for products for which they either have adopted or expect to adopt technical regulations.

Another agreement of the Uruguay Round administered by the WTO is the Agreement on the Application of Sanitary and Phytosanitary Measures (SPS agreement). This agreement pertains to those measures intended: (1) To protect animal or plant life or health within a territory from risks arising from the entry, establishment, or spread of pests, diseases, disease-carrying organisms, or disease-causing organisms; (2) to protect human or animal life or health within a territory from risks arising from additives, contaminants, toxins, or disease-causing organisms in foods, beverages, or feedstuffs; (3) to protect human life or health within a territory from risks arising from diseases carried by animals, plants, or products thereof, or from entry, establishment, or spread of pests; or (4) to prevent or limit other damage within a territory from the entry, establishment, or spread of pests.

In order to harmonize SPS measures on as wide a basis as possible, the SPS agreement encourages Members to base their SPS measures on international standards, guidelines, or recommendations. Thus, the SPS agreement, like the new TBT agreement, encourages use of international standards. The SPS agreement refers specifically to standards established by the Codex Alimentarius Commission, as discussed below.

NAFTA also contains TBT and SPS agreements similar to those in the new WTO agreements.

2. Internal U.S. Government Policy

The United States Office of Management and Budget (OMB), in its revision to OMB Circular No. A–119 (58 FR 57643, October 26, 1993), provides policy on Federal use of standards and agency participation in voluntary standards bodies and standards-developing groups:

''It is the policy of the Federal Government in its procurement and regulatory activities to:

a. Rely on voluntary standards, both domestic and international, whenever feasible and consistent with the law and regulation pursuant to law;

b. Participate in voluntary standards bodies when such participation is in the public interest and is compatible with agencies' missions, authorities, priorities, and budget resources; and

c. Coordinate agency participation in voluntary standards bodies so that: (1) The most effective use is made of agency resources and representatives; and (2) the views expressed by such representatives are in the public interest and, as a minimum, do not conflict with the interests and established views of the agencies.''

OMB Circular No. A–119 also establishes additional policy guidance and responsibilities for U.S. Government agencies. It is applicable to all executive agency participation in voluntary standards activities, domestic and international, but not to activities carried out pursuant to treaties and international standardization agreements.

The term ''standard,'' as defined in OMB Circular No. A–119, means:

''* * * a prescribed set of rules, conditions, or requirements concerned with the definition of terms; classification of components; delineation of procedures; specification of dimensions, materials, performance, design, or operations; measurement of quality and quantity in describing materials, products, systems, services, or practices; or descriptions of fit and measurement of size.''

The circular defines ''voluntary standards'' as:

''* * * established generally by private sector bodies, both domestic and international, and are available for use by any person or organization, private or governmental. The term voluntary standard includes what are commonly referred to as ''industry standards'' as well as ''consensus standards,'' but does not include professional standards of personal conduct, institutional codes of ethics, private standards of individual firms, or standards mandated by law, such as those contained in the United States Pharmacopeia and the National Formulary, as referenced in 21 U.S.C. 351.''

These definitions in OMB Circular No. A–119 conform to common usage and are consistent with the usage of these terms throughout this policy document. It should be noted that, under the TBT, ''standards'' are considered to be nonmandatory (i.e., voluntary) unless promulgated into mandatory technical regulations.

II. Standards Programs and Practices Within FDA

A. Purpose of FDA Involvement in Standards

The central purpose of FDA involvement in the development and use of standards is to assist the agency in fulfilling its public health, regulatory mission. The agency intends to participate in the development of standards, domestic or international, and adopt or use standards when such action will enhance its ability to protect consumers and the effectiveness or efficiency of its regulatory efforts. In doing so, FDA recognizes that standards often serve as useful adjuncts to agency regulatory controls and that economies of time and human resources are often realized in solving problems when consensus-building activities are undertaken and conducted in open, public arenas. The working together of FDA staff with other professionals outside the agency in standards bodies effectively multiplies the technical resources available to FDA. Further, standards bodies generally have in place procedures for periodically reviewing and updating completed standards, thus extending the resource-multiplier effect, as well as keeping the solutions current with the state of knowledge. The economy of effort translates into monetary savings to the agency, regulated industries, and ultimately consumers. Further, using standards, especially international ones, is a means to facilitate the harmonization of FDA regulatory requirements with those of foreign governments, to better serve domestic and global public health.

Another benefit of participating in the development of standards at both domestic and international levels is that in sharing technical information with technical groups and professionals outside FDA, staff members have opportunities to learn of other viewpoints on an issue, to establish scientific leadership, and to remain informed of state-of-the-art science and technology.

B. Past and Present Activities

FDA has been involved in standards activities for many years, and on January 25, 1977, the agency promulgated a final regulation, now found at 21 CFR 10.95 (§ 10.95), covering the participation by FDA employees in standards-setting activities outside the agency. This regulation encourages FDA participation in standard-setting activities that are in the public interest and specifies the circumstances under which FDA employees can participate in various types of standards bodies.

Standards activities of multilateral organizations such as the World Health Organization (WHO) and the Organization for Economic Cooperation and Development (OECD, an international organization with 25 member countries with advanced industrial economies) are often important to FDA and frequently involve multiple product types. For example, OECD is developing Genetic Toxicology Test Guidelines that are of interest to all FDA Centers. Similarly, guidelines developed under the International Programme on Chemical Safety of the WHO relate to chemicals that may be in a wide variety of FDA-regulated products, such as food additives, pesticides, drugs, animal drugs, biologics, and devices. The United States Pharmacopeia is a national standard setting body in which FDA officials actively participate.

The principal standards organizations that are not connected with a treaty are the International Organization for Standardization (ISO) and the International Electrotechnical Commission (IEC). Private organizations and government agencies, including FDA, participate in ISO and IEC activities through the American National Standards Institute (ANSI). ANSI represents the United States in the ISO and IEC and coordinates much of the standards development activity in the United States. As discussed below, FDA is active in many ISO, IEC, ANSI, and standards development organization activities. For example, FDA is represented on the Board of Directors of ANSI and on several of its committees and working groups.

1. Foods and Veterinary Medicine

FDA's Center for Food Safety and Applied Nutrition (CFSAN) and Center for Veterinary Medicine (CVM) actively participate in the development of international standards by the Codex Alimentarius Commission (Codex). Codex is an international organization formed in 1962 to facilitate world trade in foods and to promote consumer protection. It is a subsidiary of two United Nations components, the Food and Agriculture Organization (FAO) and the WHO. Codex standards cover food commodity standards (similar to FDA standards of identity), food additives, food contaminants, and residues of veterinary drugs in food. FDA officials chair two Codex committees, the Food Hygiene Committee and the Residues of Veterinary Drugs in Foods Committee, and participate in many others. Through its involvement, FDA has been influential in the establishment of many Codex standards. FDA's procedures for reviewing Codex standards for purposes of regulation are codified in 21 CFR 130.6 and 564.6.

A provision of the United States implementing legislation for the Uruguay Round Agreements, Pub. L. 103–465, requires the President to designate an agency to inform the public, through a notice published in the **Federal Register** each year by June 1, of certain Codex Alimentarius standard-setting activities. The President, pursuant to Proclamation No. 6780 of March 23, 1995 (60 FR 15845, March 27, 1995), designated the Department of Agriculture to have this responsibility, and the first such notice of Codex activities was published in the **Federal Register** of May 23, 1995 (60 FR 27250).

In 1988, the governments of the United States and Canada entered into the Canada-United States Free Trade Agreement (now largely superseded by NAFTA). Since then, officials from CFSAN and CVM have participated in technical working groups responsible for implementation of the chapter of the agreement that deals with agriculture, food, beverage, and related goods (the CUSFTA Technical Working Groups).

Officials from CFSAN and CVM also participate in the development of standards by such domestic and international groups as the Food Chemicals Codex (FCC), AOAC International (previously, the Association of Official Analytical Chemists), expert committees of the WHO, FAO, ISO, and other international consensus standards bodies. Standards developed by these organizations are used by industry, both in the United States and abroad. These standards provide industry with guidance for food grade materials and processes, and thus help elevate the quality of food and food chemicals in domestic and international trade.

CFSAN has adopted many FCC and American Society for Testing and Materials (ASTM) standards and AOAC methods, incorporating them into regulations for both food additives and generally recognized as safe food ingredients. CFSAN also refers industry to relevant FCC, Codex, or ASTM standards when discussing particular issues related to good manufacturing practices. CFSAN accepts many AOAC and equivalent methods for use by laboratories in assaying food and in testing for contaminants in food.

CVM accepts many AOAC and equivalent methods for use by laboratories in testing for drug residues in animal tissues. CVM has adopted the consumption estimates used by the FAO/WHO Joint Expert Committee on Food Additives in the development of standards for drug residues in animal tissues.

CVM is also an active participant in a new harmonization effort under the auspices of the Office of International Epizooties (OIE). This activity is known as the International Cooperation on Harmonisation of Technical

Requirements for Registration of Veterinary Medicinal Products (VICH).

2. Biologics and Drugs

There has been active international standard setting for biological products for more than 50 years. Officials from FDA's Center for Biologics Evaluation and Research (CBER) serve as experts or members of a variety of international committees that perform standard-setting functions. Activities have encompassed collaborative studies to establish international units of measure and to develop internationally accepted standards for control of biologics, including WHO standards. Efforts have been directed to many kinds of biological products, including vaccines, human blood and plasma products, blood testing reagents, and allergenic extracts, and have extended to biotechnology-derived growth factors, cytokines, and monoclonal antibody products.

FDA's Center for Drug Evaluation and Research (CDER), CBER, and the National Center for Toxicological Research (NCTR) actively participate in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). This ongoing project, begun in 1989, has been undertaken by governmental agencies responsible for regulation of drugs and by industry trade organizations from the European Union (EU), Japan, and the United States. Specifically, ICH is sponsored jointly by the Commission of the European Communities (CEC), the Japanese Ministry of Health and Welfare (MHW), FDA, the European Federation of Pharmaceutical Industries' Associations (EFPIA), the Japan Pharmaceutical Manufacturers Association (JPMA), and the Pharmaceutical Research and Manufacturers Association (PhRMA) of the United States. In addition, the International Federation of Pharmaceutical Manufacturers Associations (IFPMA) participates as an umbrella organization for the pharmaceutical industry and provides the secretariat function for ICH. ICH operates under the direction of the ICH Steering Committee, which is comprised of representatives of these organizations. Official observer status has been given to WHO, the European Free Trade Area (EFTA), and the Health Protection Branch of Canada.

The purposes of ICH are to: (1) Provide a forum for a dialogue between regulatory agencies and the pharmaceutical industry on differences in the technical requirements for product registration (i.e., requirements for product marketing) in the EU, Japan, and the United States; (2) identify areas where modifications in technical requirements or greater mutual acceptance of research and development procedures could lead to more efficient use of human, animal, and material resources without compromising safety, quality, and efficacy; and (3) make recommendations of practical ways to achieve greater harmonization in the interpretation and application of technical guidelines and requirements for registration. The work products of ICH, created in working groups of experts from the regulatory agencies and industry, consist of a series of consensus guidance documents. These guidance documents, after successive ICH steps of review and acceptance, including an opportunity for public review and comment in the respective jurisdictions, are forwarded to the regulatory agencies with the expectation that they will be formally adopted by the agencies.

Officials from both CBER and CDER also participate in a consensus standard setting activity sponsored by the Council for International Organizations of Medical Sciences (CIOMS) that is aimed at standardizing medical definitions and adverse experience reporting.

3. Medical Devices and Radiation-Emitting Products

FDA's Center for Devices and Radiological Health (CDRH) has had extensive involvement with standards in its regulation of medical devices, as well as electronic products that emit radiation. The development of standards to solve problems related to medical devices involves many groups outside FDA. The interaction between CDRH and the manufacturing and health care communities that frequently occurs during the standards development process provides knowledge and insight into the use of products, problems, and the effectiveness of solutions. Frequently, the public discussion of the problem that occurs in the consensus-building process results in the manufacturers and the users of the subject medical device implementing the solution before a standard is formally completed. Thus, CDRH has encouraged participation in the development of standards as a useful adjunct to regulatory controls. CDRH's approach to use and participation in the development of consensus standards was described in a letter dated June 29, 1993, to all interested parties from the Director of CDRH. (This policy did not apply to mandatory performance standards, i.e., technical regulations, for class II medical devices as specified under the Medical Device Amendments of 1976 (Pub. L. 94–295). The Safe Medical Devices Act of 1990, SMDA (Pub. L. 101–629), puts the promulgation of mandatory standards at the discretion of the agency.)

Over 200 completed consensus standards and selected sections of additional draft standards that are not yet complete have been incorporated into guidance documents for applications for conducting clinical trials with investigational devices and applications for permitting devices to be marketed. These guidance documents are widely disseminated by CDRH to all interested parties. Other standards used by CDRH, or which CDRH has helped to develop, concern measurement or test methods, or support good manufacturing practices and quality assurance.

A new ISO Committee, Technical Committee 210 (TC–210) is developing harmonized standards in these areas. Also, CDRH is an active participant in the Global Harmonization Task Force, in cooperation with officials from Canada, the EU, Japan, and other countries.

CDRH has published a notice of a working draft of a final rule to revise the current good manufacturing practice regulations for medical devices (60 FR 37856, July 24, 1995), in part to ensure that they are compatible with specifications for quality systems contained in an international quality standard developed by ISO, namely ISO 9001 ''Quality Systems Part 1. Specification for Design/Development, Production, Installation, and Servicing.'' This standard (ISO 9001) is becoming widely recognized by medical device regulatory authorities worldwide and is finding application in many other industry sectors as well. CDRH officials, working with counterpart foreign government officials, are pursuing in step-wise fashion the harmonization of quality system inspection procedures and enforcement.

The process of harmonizing regulatory requirements is facilitated by using an international standard as a basis. Such harmonization is not only recognized public policy, but for medical devices, it is explicitly encouraged by provisions of SMDA (Pub. L. 101–629), which states, in part, that FDA ''* * * may enter into agreements with foreign countries to facilitate commerce in devices between the United States and [foreign] countries consistent with the requirements of this Act.'' 21 U.S.C. 383.

In a recent (April 1995) program review, CDRH reported that in 1994, 192 Center staff members served as primary and alternate liaison representatives on 440 committees and subcommittees in 38 standards developing organizations (domestic and foreign). CDRH actively reviewed 286 draft standards; of these, 134 were with nine international standards organizations. The experience CDRH has acquired over the years has provided the foundation for the standards policy it announced on June 29, 1993. The essential features of that policy are reflected in the FDA policy presented in section IV. below.

4. Regulatory Affairs

FDA's Office of Regulatory Affairs (ORA) is increasingly active in international standards activities relevant to quality control and conforming assessment, including activities relevant to ISO—9001 and laboratory regulation.

III. Response to Comments

In response to its request for comments on the draft international harmonization policy on standards, FDA received comments from ten organizations (standards setting organizations, trade and professional associations, a manufacturer, and a consumer organization). A discussion of the comments received and the agency's responses follow.

1. In general, the comments supported the agency's proposed international harmonization policy on standards. For example, one comment stated that the policy demonstrated the agency's commitment to the international standards development process as well as international harmonization. Another comment pointed out that the policy will better enable the agency to establish agreements with other global regulatory bodies, and ultimately permit FDA to carry out its mandate to protect the public health in a more efficient and cost effective manner. Other comments stated that the harmonization of regulatory requirements and supportive standards could benefit U.S. companies engaged in international trade. In addition, one of these

comments pointed out that standards reflect technology, and that the first priority with regard to standards should always be to develop standards that represent the best available technological solutions, adding that 'harmony' and 'consistency' can be achieved through the general acceptance of excellent technological solutions. FDA agrees with these comments.

A. Potential for Lowered Standards

2. Two comments stated that harmonization has the potential to result in lowered standards, with potential adverse effects on public health protection. One of the comments expressed concern that FDA was subordinating the public interest in favor of voluntary standards bodies and standards developing groups in a manner that is inconsistent with the vital tasks assigned to the agency to protect health. The second comment argued that the first priority with regard to standards should be to develop standards that represent the best available technological solutions, and that FDA should not support international standards that reflect inferior or compromised technological solutions that become obstacles, rather than benefits, to U.S. industry. Another comment, while agreeing that international standards should be adopted as national standards whenever possible, stated that international standards may sometimes not meet the needs of our health care community, adding that some may contain safety standards only and no performance parameters, and that the international standards may also be inconsistent with our country's codes and regulations.

FDA wishes to reassure those who commented that FDA's participation in international harmonization activities is intended to safeguard the U.S. public health and to assure that consumer protection standards and requirements are met. Indeed, a central principle that guides the agency's international harmonization activities is that the activities should further FDA's mission to protect the public health. In addition, international agreements to which the U.S. Government is a party have provisions that ensure that harmonization activities will not result in lowered standards. For example, the WTO Agreement on SPS provides that each country may determine its appropriate level of protection; therefore, the encouragement to use international standards as the basis for technical regulations will not result in ''downward harmonization.'' Safeguards have been built into the TBT agreement and U.S. implementing legislation that protect the ability of each country to establish requirements necessary to fulfill a legitimate objective. As stated in section I.C.1. above, the implementing legislation for the new TBT agreement, which provides additional authority for FDA's international standards activities, provides further assurance that such harmonization would not result in lowering safety or quality standards for U.S. consumers. Thus, the agency does not agree that harmonization will result in inferior standards. Furthermore, FDA's participation in standards development, consistent with § 10.95 and OMB Circular No. A–119, and FDA's use of standards in its regulatory programs, will be dependent not only on the substantive aspects of the standards for ensuring the safety, effectiveness, and quality of products, but also on the development process for the standard. The standard itself must also comply with all applicable statutes, regulations, and policies.

B. Regulatory Issues

3. One comment stated that any time a voluntary standard is used in a regulation, the scope of that standard needs to be unambiguously determined. The comment used a hypothetical case of a voluntary standard intended to be used in the home environment being inappropriately extended to the hospital environment. The comment argued that if the regulatory need exceeds the scope of the existing voluntary standard, it may indicate the need for yet another voluntary standard that addresses the additional scope, or else provisions may need to be added to the existing voluntary standard so as to accommodate the broader scope in which the standard is to be applied.

The agency agrees that when a voluntary standard is used in a regulation, the scope of that standard should be unambiguously expressed. As stated above, a basic tenet in the development and adoption of a standard is that it contributes to safer, more effective, and higher quality products. Inappropriate application of a standard (voluntary or as part of a technical regulation) would run counter to this notion.

4. Three comments questioned the need to make voluntary standards mandatory regulations. One of the comments stated that if the agency uses a voluntary standard as a ''referee'' standard, which means that the agency uses the voluntary standard as a frame of reference for determining safety and efficacy, there should be no need for the agency to go through the procedures required for creating a regulation. The second comment stated that if technical standards are based on state-of-the-art science and are revised as needed to incorporate advances, they should be voluntary standards as opposed to regulatory requirements. The third comment asserted that existence of a standard does not warrant a regulation and FDA should avoid unnecessary regulations.

The agency agrees that it should avoid unnecessary regulations but notes that there are times when it finds it is necessary to propose and promulgate regulations for the efficient enforcement of the laws it administers. Voluntary standards that will serve agencies' purposes and are consistent with applicable laws and regulations can be adopted and used by Federal agencies. This principle is stated in both FDA's policy and in section 7(a) of OMB Circular No. A–119 on Reliance on Voluntary Standards. Thus, when appropriate, FDA will adopt voluntary standards by referencing them in the regulations it promulgates. In all other instances, these standards will remain voluntary.

As stated above, the purpose of FDA's involvement in the development and use of standards is to assist the agency in fulfilling its public health and regulatory missions. Thus, the agency intends to participate in the development of domestic and international standards, and to adopt or use standards, when such action will enhance its ability to protect consumers and the effectiveness or efficiency of its regulatory efforts.

C. Transparency

5. Four comments addressed the need for transparency during the development of standards, in determining ''official'' use of a standard, or when standards are used in a regulation or adopted as regulations. The comments asserted that, if voluntary standards are incorporated into guidance documents and compliance policy guides and serve as the bases for mandatory standards and other regulations promulgated by FDA, ample opportunity should be provided for interested parties to comment through the established procedures of notice and comment rulemaking. One comment further stated that the policy should include a statement of assurance that FDA will engage potentially affected parties whenever it intends formal inclusion of a voluntary standard in an FDA document or process.

The agency agrees that the development of standards should be conducted in an open fashion. Under § 10.95, one of the criteria for FDA participation in standards-setting bodies is that the group or organization responsible for the standard-setting activity must have a procedure by which an interested person will have an opportunity to provide information and views on the activity and standards involved, and that the information and views will be considered. This is why FDA clearly states in its policy (section IV. below) that one of the factors for FDA's participation in standards development and use is the transparency of the process, i.e., the process must be open to public scrutiny and provide the opportunity for the consideration of views of all parties concerned.

With regard to transparency when standards are used in a regulation or adopted as regulations, under the Administrative Procedure Act (APA), an agency that issues, amends, or revokes a regulation, whether on its own initiative or when petitioned by an interested person, must act in an open manner with adequate time provided for comment from interested parties, which will be considered before a final regulation is promulgated. FDA's rule on promulgation of regulations, found in 21 CFR 10.40, is explicit with respect to the need for transparency of the process and opportunity for participation in the process by interested persons. Other procedural regulations govern guidelines and similar documents (21 CFR 10.90), and interested persons may use correspondence or meetings (21 CFR 10.65), petitions (21 CFR 10.30), or reviews by supervisors (21 CFR 10.75) to raise issues and present views about other nonbinding guidance documents, which provide industry with useful information about recommended or alternative ways to comply with requirements. In fact, FDA has increasingly used public meetings to elicit and share information with regard to its guidance documents and it currently is reviewing the procedures it uses to develop guidance documents to ensure sufficient transparency in the process.

Thus, with regard to the comment that this policy should include a statement of

assurance that FDA will engage potentially interested parties whenever it intends formal inclusion of a voluntary standard in an FDA document or process, the agency finds that it is not necessary to do so as part of this document because there are established mechanisms under the APA and the agency's administrative practices and procedure regulations for obtaining and considering views of interested persons. Of course, FDA is not foreclosing future consideration of additional mechanisms toward this end.

D. Comments on Specific Issues

6. One comment suggested the alternative language, ''The standard contributes to safe and effective products that meet consumers' requirements for quality,'' instead of ''The standard contributes to safer, more effective, and higher quality products'' (section III.A.1., proposed policy) and ''The standard, if adhered to, would help ensure the safety, effectiveness, or quality of products'' (section III.D.1., proposed policy). The alternative language was offered to simplify future negotiations and to allow the agency to participate more fully in standards development and promulgation. The comment also questioned the use of the terms 'safer' and 'more effective' in section III.A.1. of the proposed policy (see above) because it is not clear what the measures for 'safer' and 'more effective' are. The comment further stated that the term ''higher quality'' is relative, leaving open to question who determines higher quality. Finally, the comment added that an international standard could conceivably result in requirements for the same degree of safety, effectiveness, and quality as those required by FDA.

The agency is revising the policy in a manner similar to that suggested by the comment. FDA agrees that an international standard could indeed result in requirements for the same degree of safety, effectiveness, and quality as required by FDA. In fact, one of FDA's guiding principles in its international harmonization activities is that FDA should accept, where legally permissible, equivalent standards of other countries provided such standards meet FDA's goals to facilitate the availability of safe, effective, and properly labeled products. The agency further agrees that the alternative language would allow the agency more flexibility to participate in standards development, without compromising public health, and is therefore amending the policy accordingly.

7. One comment supported FDA's intent to develop standards on the basis of sound scientific and technical information. The comment added that the use of sound scientific and technical information will permit the development of food regulations and standards that cannot be misconstrued as unreasonable trade barriers. However, the comment cautioned that a decision on participation in standards development should be based on the purpose of the standard, not whether the standard is based on sound scientific and technical information.

The agency agrees that while all standards should be based on sound scientific and technical information, not all scientifically sound standards will serve purposes justifying the agency's participation in developing them. FDA's regulation on participation in outside standard-setting activities states that not only will the activity be based upon consideration of sound scientific and technological information, but it also will be designed to protect the public against unsafe, ineffective, or deceptive products and practices (21 CFR 10.95(d)(5)(i)). In addition, OMB Circular No. A–119 states that it is the policy of the Federal Government to participate in voluntary standards bodies when such participation is in the public interest and is compatible with agencies' missions, authorities, priorities, and budget resources. The OMB Circular adds that the providing of agency support to a voluntary standards activity should be limited to that which is clearly in furtherance of an agency's mission and responsibility. These directives are adequately reflected in the policy.

8. One comment suggested that proposed section III.A.4., ''The development of an international standard that achieves the agency's public health objectives is generally, but not always, given a higher priority than the development of a domestic standard,'' be deleted because it is made clear in other parts of the draft policy that FDA complies with U.S. obligations under the GATT, other international trade agreements, and OMB Circular No. A–119.

The agency agrees that the draft policy document does make clear that FDA complies with U.S. obligations under international agreements and the OMB Circular. However, the agency does not agree that proposed section III.A.4. should be deleted. FDA's belief that the development of an international standard that achieves the agency's public health objectives is generally (but not always) given a higher priority than the development of a domestic standard, is an important factor on which agency participation in standards development is based and merits being clearly delineated. This is more so because proposed section III (section VI. of this document), FDA Policy on Standards, is intended to stand on its own as the agency's policy on harmonization of standards and, therefore, needs to be as complete as possible.

FDA emphasizes that there are three routes to development of a harmonized international standard, all of which are favored under the FDA policy: (1) The U.S. voluntary standards community or an agency, such as FDA, develops a U.S. standard and takes it to an international forum so it can be made an international standard; (2) a standard already developed in an international forum (or by another country or a regional standards body) is adopted as a U.S. voluntary or regulatory standard; or (3) a new international standard is developed, ''from scratch,'' in an international forum. Which of these routes is followed in the particular case will vary with the facts of that case. While starting a standards activity in an international forum offers many efficiencies in avoiding duplication of effort, there will continue to be times when it makes sense first to develop a domestic standard (voluntary or regulatory) and then to take it, as appropriate, to an international forum.

9. One comment asserted that the intent of proposed factors III.A.6. and III.D.6., which state: ''Wherever appropriate for the product, the standard stresses product performance rather than product design, but where necessary, covers all factors required to ensure safety, effectiveness, and quality,'' was not clear. The comment added that inspection can be used to prevent poor quality products from being consumed but that safety cannot be inspected into a product. The comment stated further that safety must be designed into products during development, subsequent manufacturing, packaging, and transport. Further, the comment stated that product performance or product functionality issues with regard to safety are the primary focus in the development of food regulations, and therefore, the comment recommended alternative language to that in the proposed policy: ''Wherever appropriate for the product, the standard stresses product safety, performance, and functionality, but where necessary, covers all factors required to ensure safety and effectiveness, including product and process design, and process performance.''

The agency believes that the suggested language is helpful in capturing FDA's intentions in formulating these factors as the basis for participation in standards development, and use of standards in its regulatory programs. Therefore, the agency is making editorial changes in the factors along the lines suggested in the comment.

E. Other Comments

10. One comment recommended that FDA review and revise current U.S. guidelines for toxicity testing of food additives as outlined in the *Toxicological Principles for the Safety Assessment of Direct Food Additives and Color Additives Used in Food (Redbook I)*, as well as the proposed guidelines set forth in the revised draft, *Redbook II*, and harmonize with those recommended by the OECD. The comment added that this will allow more universal acceptance of results performed throughout the world and will minimize the need to repeat expensive testing to meet different testing standards in different countries.

The agency has stated that standards activities of organizations such as OECD are often important to FDA, and that the development of international standards, and harmonization with international standards if they achieve the agency's public health objectives, will in most instances be given a high priority.

The agency announced that the draft *Redbook II* was available (March 29, 1993, 58 FR 16536) and solicited comments on the draft revised guidelines. *Redbook II* is being finalized in light of comments received by the agency, including a comment that the guidelines should be harmonized with those of the OECD; the final revised *Redbook II* has yet to be issued. The agency notes that, in revising the guidelines in the *Redbook*, it took into account the fact that differences among guidelines can result in unnecessary duplication of effort and inefficient use of

scarce testing resources. The agency also wants to make clear that the *Redbook* is designed to provide guidance. Strict adherence to *Redbook* guidelines is not a requirement for toxicological studies conducted to establish the safety of an additive.

11. One comment indicated concern that a long standing participation by the United States Public Health Service in the 3–A Sanitary Standards (for dairy and related food industries) is not mentioned in the text of the draft policy. The comment also stated that it is necessary that, as international agreements anticipate trade and importation of equipment, compliance with 3–A Sanitary Standards should be applied by reference to assure receipt of acceptable equipment.

The domestic and international standards-setting organizations or bodies listed under section II.B. of this document are those in which FDA has been or is most actively involved in developing standards. The listing is not meant to be exhaustive nor is it meant to list all standards setting bodies in which FDA has an interest.

12. One comment urged FDA to reference voluntary standards rather than adopting and publishing standards, to maintain appropriate support for standards development. The comment argued that referencing rather than publishing the text of voluntary standards as regulations or guidance protects the standards organizations' copyrights which provide the financial support for national and international programs.

FDA uses standards in the manner described in OMB Circular No. A–119, which states that while voluntary standards adopted by Federal agencies should be referenced along with their dates of issuance and sources of availability in appropriate publications, regulatory orders, and in related in-house documents, such adoption should take into account any applicable requirements of copyright law and other similar restrictions.

13. One comment advised that the value of standards is that they are the consensus product of all technology experts, not just the consensus of experts from government. Therefore, care should be exercised that government participation in voluntary standards organizations and its use of voluntary standards does not lead to an appearance that voluntary standards organizations are unduly directed or influenced by government.

The agency is sensitive to the need for balanced participation in voluntary standards bodies and works within OMB's guidelines regarding policy to be followed by executive agencies in working with voluntary standards bodies. OMB Circular No. A–119 states that agency representatives serving as members of standard-developing groups should participate actively and on a basis of equality with private sector representatives but that, in doing so, agency representatives should not seek to dominate such groups. In addition, the number of individual agency participants in a given voluntary standards activity should be kept to the minimum required for effective presentation of the various program, technical, or other concerns of Federal agencies. Finally, while the circular encourages agency representatives to participate in the policy-making process of voluntary standards bodies, particularly in matters such as establishing priorities, developing procedures for preparing, reviewing and approving standards, and creating standards-developing groups, it also states that in order to maintain the private, nongovernmental nature of such bodies, agency representatives should refrain from decisionmaking involvement in the internal day-to-day management of such bodies.

F. Conclusion

Therefore, after considering the comments received, FDA is issuing this statement of policy.

IV. FDA Policy on Standards [1]

It is the intent of this policy to enable FDA to: (1) Continue to participate in international standards activities that assist it in implementing statutory provisions for safeguarding the public health, (2) increase its efforts to harmonize its regulatory requirements with those of foreign governments, including setting new standards that better serve public health, and (3) respond to laws and policies such as the Trade Agreements Act and OMB Circular No. A–119 that encourage agencies to use international standards that provide the desired degree of protection. Accordingly, it is the policy of FDA, concerning the development and use of standards, that:

A. FDA participation in standards development will be based on the extent to which the development activity and expected standard conform to certain factors, with consideration also being given to the resources available in FDA to devote to the effort and expected efficiencies to be gained as a result of the effort; the factors are as follows:

1. The standard stresses product safety and effectiveness and therefore contributes to safe, effective, and high quality products; when necessary, the standard also covers all factors required to ensure safety and effectiveness, including product and process design, and process performance;

2. The standard is based on sound scientific and technical information and permits revision on the basis of new information;

3. The development process for the standard is transparent (i.e., open to public scrutiny), complies with applicable statutes, regulations, and policies, specifically including § 10.95 and OMB Circular A–119, and is consistent with the codes of ethics that must be followed by FDA employees;

4. The development of an international standard that achieves the agency's public health objectives is generally, but not always, given a higher priority than the development of a domestic standard; and

5. The development of a horizontal standard which applies to multiple types of products is generally, but not always, given higher priority than the development of a vertical standard which applies to a limited range of types of products.

B. FDA is not bound to use standards developed with FDA participation. For example, the agency will not use a standard when, in the judgment of FDA, doing so will compromise the public health.

C. The uses of final (and selected draft or proposed) standards, or selected relevant parts, will include, where appropriate: (1) Incorporating such standards into guidance documents for nonclinical testing, applications for conducting clinical trials with investigational products, and applications for permitting products to be marketed; (2) conducting reviews of such applications; (3) incorporating such standards into compliance policy guides; (4) conducting reviews of test protocols used by firms as part of good manufacturing practices; (5) conducting reviews of study protocols submitted by firms as required for postmarket surveillance studies or programs; (6) serving as the basis for mandatory standards or other regulations promulgated by FDA; and (7) serving as the basis for reference (e.g., evaluation criteria) in a memorandum of understanding with other government agencies.

D. The use of a standard in the regulatory programs of FDA is dependent upon the following factors:

1. The standard stresses product safety and effectiveness and therefore, if adhered to, would help ensure the safety, effectiveness, or quality of products; when necessary, the standard also covers all factors required to ensure safety and effectiveness, including product and process design, and process performance;

2. The standard is based on sound scientific and technical information and is current;

3. The development process for the standard was transparent (i.e., open to public scrutiny), was consistent with the codes of ethics that must be followed by FDA employees, and the standard is not in conflict with any statute, regulation, or policy under which FDA operates;

4. Where a relevant international standard exists or completion is imminent, it will generally be used in preference to a domestic standard, except when the international standard would be, in FDA's judgment, insufficiently protective, ineffective, or otherwise inappropriate; and

5. Where a relevant horizontal standard which applies to multiple types of products exists or its completion is imminent, it will generally be used in preference to a vertical standard, which applies to a limited range of types of products, except when such horizontal standard would be insufficiently protective, ineffective or otherwise inappropriate.

E. FDA employees will comply with agency regulations (§ 10.95) covering participation in standard setting activities outside the agency.

Dated: October 4, 1995.

William B. Schultz,

Deputy Commissioner for Policy.

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