

A MODEL REGULATORY PROGRAM FOR MEDICAL DEVICES: AN INTERNATIONAL GUIDE



ESSENTIAL DRUGS AND TECHNOLOGY PROGRAM
DIVISION OF HEALTH SYSTEMS AND SERVICES DEVELOPMENT

PAN AMERICAN HEALTH ORGANIZATION
Pan American Sanitary Bureau, Regional Office of the
WORLD HEALTH ORGANIZATION

in cooperation with
UNITED STATES FOOD AND DRUG ADMINISTRATION

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FOREWORD

“WHO’s efforts to improve health and quality of life are grounded in the firm belief that in order to bring about the necessary changes, health policies must reach beyond the health sector, while remaining rooted in the health-for-all principles of primary health care. Health is becoming a central political, social and economic issue in all countries, and health concerns must therefore be taken up at the highest political level and given due consideration in all public policies.”

The World Health Report, 1995

Maintaining and improving human health are noble goals. As the world ushers in a new millennium, these dual goals are more achievable than at any time in our history given the advent of medical technology. Although medical technology has emerged as an integral part of health care, it poses a number of unique challenges. Foremost among these challenges is assuring that medical devices, like human drugs and vaccines, are produced properly and are used judiciously and safely so that patients can reap the benefits of mankind’s miraculous inventions.

As technologies become more complex, the role of medical devices in health care is constantly being re-defined, as is the role of governmental public health bodies. Some countries around the world have substantial experience in regulating the full gamut of medical device research, development, manufacturing, distribution and use. Others have more limited rules that apply only to certain aspects of devices. Still others have no controls pertaining to medical devices. It is the latter audience that this document is especially designed to reach.

I commend this document to your attention. Its purpose is to assist you in deciding what governmental controls, if appropriate, are best suited for your nation’s health care situation.

I wish to recognize and thank Mr. Robert C. Eccleston, Assistant to the Director in the U. S. Food and Drug Administration’s Center for Devices and Radiological Health. Mr. Eccleston authored this document in 1996 as a part of an FDA-supported consultancy for WHO. He later provided expert assistance to PAHO officials as they prepared the document for publication.

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PREFACE

In the span of three decades, medical devices—from the most basic to the most sophisticated—have become an indispensable part of the world’s medical diagnostic and therapeutic armamentarium. With each passing year, advancements in medical technology make it increasingly imperative for governments to promulgate laws and regulations or undertake other public health measures to ensure that maximal benefits are derived from their use while risks to patients are kept to a minimum.

This document and the model program it offers represent an effort towards that end. In 1986, the World Health Organization (WHO), the Pan American Health Organization (PAHO) and the United States Food and Drug Administration (FDA) co-sponsored an International Conference of Medical Device Regulatory Authorities. The conference’s primary goal was to be a “significant first step towards the promotion of exchange of information and closer communication and cooperation among countries.” On October 20-22, 1999, PAHO sponsored an expert consultation on medical device regulation with senior representatives from the U.S. FDA, Health Canada’s Medical Devices Bureau and ECRI, among other organizations.

This document, which as noted previously was initially written by Mr. Robert C. Eccleston as an FDA consultant to WHO, has been revised in accordance with comments received from PAHO Member States and experts from the medical device field. In addition to Mr. Eccleston, the following professionals from the U. S. Food and Drug Administration contributed to the final preparations of this document: Ms. Linda Horton, Ms. Minna Golden, Mr. John Stigi, Mr. Steven Niedelman, Mr. Larry Spears, Ms. Deb Yoder Blum, Mr. Timothy Ulatowski, Ms. Christine Nelson, Dr. Jerome Donlon, Mr. Les Weinstein and Mr. Wes Morgenstern. PAHO expresses appreciation to these persons for their invaluable assistance.

PAHO also wishes to acknowledge the exemplary work of the Global Harmonization Task Force (GHTF), which is referenced in various locations throughout this document. In keeping with a Resolution CD42.R10 endorsed in 2000 by the PAHO 42nd Directive Council supporting and promoting the goals of international harmonization of medical device regulatory requirements, this document identifies key areas where GHTF guidance documents may be used to supplement information provided herein.

The document is designed to give countries in pursuit of regulatory or other controls for medical devices the guidance and information necessary to establish programs based on individual needs and capacities. It is not intended to

supplant or usurp any ongoing efforts to regulate medical devices in countries where WHO and PAHO traditionally have provided consultative assistance. To the contrary, it is offered as a suggested “blueprint” for countries that have already decided or may decide in the future to embark upon medical device programs designed to better safeguard public health.

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NOTE TO USERS OF THE GUIDE

It may be useful at the outset to outline the purpose of this international program guide on medical devices. Although medical devices are used by providers of health care throughout the world, relatively few of the world's community of nations have systems in place to assure the safety and efficacy of the wide variety of products, both in terms of their production and use. In fact, in the vast majority of countries, medical devices, either imported or domestically produced, are free of any kind of independent and impartial scrutiny. This leaves health professionals and patients to fend for themselves in deciding which devices will perform as intended and which can be used safely and effectively in medical diagnostic and therapeutic procedures.

This document seeks to help fill this void. For government institutions endeavoring to establish medical device programs—regulatory or non-regulatory—this guide is intended to provide the basic “tools” to complete the task. It also outlines various issues and options countries should weigh carefully in fashioning programs to insure safe and high quality medical devices. Finally, this document serves as an informational resource to assist national officials in obtaining concrete information on a host of issues relating to medical device regulation.

It should be emphasized that this document is not a textbook on how to perform technology assessment. Nor is it a tutorial on how to procure medical devices or a prescription for filling the basic medical equipment needs of any given country. It does not examine the impact of medical device regulation on trade, economic development or overall societal costs. Finally, this document does not offer value judgments on any national regulatory system now in operation.

Rather, this document should be viewed strictly as a suggested framework that can be modified in accordance with national policies or laws, as well as any relevant resource and support structure constraints. It should also be pointed out that in several locations throughout the report, the terms “regulation” and “regulatory” are used. While in most contexts these terms have very definite and somewhat limited meanings, it is intended for the purpose of this document that they be broadly defined. That is to say, “regulation” encompasses more than strict requirements mandated by a government body. It includes other public health measures aimed at ensuring the safety and clinical effectiveness of medical devices in their broadest context.

The U. S. Food and Drug Administration supports the overall purpose of this publication and applauds the efforts of the Pan American Health Organization and World Health Organization to promote implementation of effective national

medical device regulatory systems. However, this general support is not, nor should it be construed as, a formal endorsement by the agency of any of the specific material contained herein.

Should you have questions about any of the material provided in this document, you are encouraged to contact either of the people listed below.

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INTRODUCTION

It is a truism that medical technology, in varying degrees, has permeated health care delivery systems throughout the world. Major advances after World War II in electronics, computerization, biomaterials and other scientific and technical fields led to the development of life-saving, life-supporting and other critical devices at a staggering pace. Indeed, more than 50,000 different types of devices are now being distributed in world trade. This technological revolution, which has saved lives and improved the quality of life for millions of people, continues today and should continue on into the foreseeable future.

This post-war phenomenon theoretically knows no geographic boundaries. Globally, it is estimated that the market for medical devices is growing steadily at 7 percent (1993 estimate) compared to a 1.2 percent growth rate for the world economy for the same time period. Expansion of the world market is the particular result of rapidly-emerging markets in Asia and regions in Latin America. In these areas alone, the rate of market growth is roughly three to four times higher than for the United States, Japan and Europe. Nevertheless, the availability of innovative, safe and clinically effective medical devices to the world's population is not universal. This variability in access to even basic medical technologies exists from continent to continent, country to country, locale to locale and population group to population group.

At the same time, the types and levels of regulatory controls to safeguard consumers from unsafe and ineffective medical devices, if they exist at all, also vary significantly around the world. While efforts are presently underway among some industrialized nations with medical device regulatory systems to harmonize their requirements to spur global competitiveness and provide for better husbandry of scarce regulatory resources, many if not most of the world's developing countries have no regulatory requirements for medical devices, whether imported or produced domestically, to protect their citizens.

This document provides a framework to assist Member States in establishing regulatory programs for medical devices. Because of the differences in socioeconomic conditions that exist among countries that may pursue device regulatory programs and their infrastructural capacities to implement them, the model program contained in this document is, by necessity, relatively general. It is also designed in a modular format to give interested nations the flexibility to adapt those elements of the model that best serve their individual needs and which they are best able to support.

The hope for this document is that it will serve as a useful guidepost for nations presently without medical device regulatory systems: in other words, to

equip them with the information necessary to get them started in a positive and internationally-compatible direction, one that will have beneficial societal impacts and enhance public health and safety. The document is based, although not totally, on the experiences of industrialized sectors of the world which have established comprehensive regulatory programs for medical devices. It draws upon what has worked for those nations so that readers may benefit from their experiences.

SECTION I

Guiding Principles and Essential Features of A Regulatory Program For Medical Devices

A. GUIDING PRINCIPLES

Preceding any discussion of what constitutes an effective medical device regulatory system must be the identification of the goals and guiding principles of such a program. National regulatory programs for consumer goods, including medical devices, are driven by a panoply of interests: for example, ensuring public safety, promoting trade, encouraging marketplace competition and ensuring timely availability of and access to state-of-the-art technologies and treatment modalities.

Although some of these factors may have had a bearing on the formulation of device regulatory systems now operating in various industrialized nations, the goal of protecting public health and safety is common to all. It is important to note, however, that in striving to meet this goal, some trade-offs are inevitable. Regulatory decision-making in general, as is true for medical devices, must occur against the backdrop of known risks and benefits.

It is a given that nothing in society is perfectly safe. With medical devices and many other consumer products, societies must learn to cope with and understand that some level of risk is not only acceptable but inevitable in order to realize and reap the benefits of their use.

Absolute safety cannot be guaranteed or ever attained. Nor can any regulatory system assure that a product will endure and perform optimally forever or that effectiveness can be totally assured. In any rational regulatory system, relative risks must be properly balanced against expected benefits. Judgments must be made based on cultural norms, economic impacts, effects on the viability of native businesses, the availability of clinically important products and public acceptance of the premise that nothing in life is risk-free.

With this said, the following suggested tenets can be used as cornerstones of an effective medical device regulatory program.

Principle 1

The primary goal is to protect public health and safety.

This is the most fundamental goal, provided the underlying mechanisms reflect the kind of public attitudes toward risk and the need for reason and realism that were discussed previously. Accordingly, a device regulatory program must be grounded in what is reasonably achievable or, in other words, assuring that medical devices are regulated in a way that weighs probable benefits to health against the probable risk of illness or injury.

Principle 2

A regulatory system should ensure that valuable new technologies are made available to the clinical community and to patients and consumers expeditiously while preventing unsafe or ineffective devices from reaching the market.

Overzealous regulation can become a barrier to trade and an inhibitor of technological innovation. It can also be counterproductive in the sense that health care providers and their patients are deprived of valuable new products or that access to them is significantly delayed. Thus, it is advisable to construct a device regulatory system to include mechanisms for establishing thresholds of product safety and effectiveness. The feature that is common to virtually all currently-operating national device regulatory systems is the concept of classification which enables governments to regulate devices on a graduated basis depending upon the risk potential of individual products.

Principle 3

Regulatory decisions must be based on strong and clear science, free of external influences and consistent with the directives of law.

Regulation is often at the confluence of competing interests and outside forces. It involves complex interplays between regulators and regulated entities, each of whom has different objectives and values, often differing scientific judgments and varying societal values. Thus, public confidence in government regulation and in those charged to carry out regulatory programs is of paramount importance. Faith and trust in government regulation by a nation's citizenry can be sustained only if regulatory decisions are based on quality science, a sound analytical base, and fairness and honesty in dealings with the regulated industry and the public.

Principle 4

As the guarantor of public health, enforcement of the law must be vigorously, fairly and uniformly carried out and appropriate regulatory and legal actions taken against violators.

The effectiveness of any regulatory system with legal underpinnings is affected by the commitment to strong enforcement of the law by those entrusted to implement the program. Promoters of bogus devices and producers of devices

which experience unforeseen failures must be dealt with fairly, but resolutely. The public rightfully expects that government regulators will take decisive action to protect them from dangerous devices as well as from economic and scientific fraud.

Principle 5

Government-prescribed rules and procedures must be clearly articulated for those who must comply with them.

Achieving a high level of compliance from establishments subject to requirements imposed by government bodies can be heavily influenced by the clarity and openness with which a governing body conveys what is expected. In other words, the specific rules promulgated by governments should be “transparent.” Statutory, regulatory and scientific requirements must be clearly stated so industry will be fully aware of what is expected—that is, no “moving targets.” This will increase assurance among businesses which must deal with government officials that their dealings will be fair, even-handed and free of bias. Cloaking requirements in secrecy or leaving device firms to self-interpret government rules can arouse suspicion of preferential treatment between competitors. It can also become a barrier to trade because companies, unsure of whether requirements will be evenly and predictably applied, may be deterred from establishing markets in a particular country.

Principle 6

Assuring medical device safety entails more than the functioning of the device itself; it requires oversight of the use of medical devices.

Users of medical devices can have a profound effect on their safe and effective performance. Unfamiliarity with a certain technology, use of the product for clinical indications outside the scope of those specified in labeling, and disregard for contraindications are but a few examples of why devices fail despite the absence of any inherent design or manufacturing defects. It is crucial that experience gained with medical devices be shared with other users to prevent future mishaps. Documenting adverse events, with a complementary mechanism for alerting other users, should be considered essential.

Principle 7

Information on product risks must be openly communicated with health professionals and consumers.

Informing the public, broadly defined, involves conveying in understandable terms what the scientific community knows and explaining in cogent terms the range of uncertainty that remains. When people are treated fairly and honestly and in a manner that respects their ability to make thoughtful, well-reasoned decisions, they tend not to overinflate modest risks and react irrationally. Accuracy and truthfulness in product labeling, advertising, promotion, and interactions with the public will afford government regulators a better chance of explaining the risks and benefits of medical devices and gain public acceptance in the process. It will also ensure that manufacturers impart the information necessary to guide health care providers on the appropriate use of their products and guard against adverse health and economic impacts arising from the use of devices with unsubstantiated medical claims.

Principle 8

Countries instituting medical device programs should be cognizant of ongoing international harmonization efforts so as to preclude regulatory controls that conflict with actual harmonized rules and guidelines or with the spirit and goals of international harmonization.

The globalization of the medical device industry has given rise to the institution of government controls in more and more nations throughout the world in order to safeguard the health and safety of their individual populations. However, due to differing laws, regulatory interpretations and implementation approaches, international commerce has been hindered. Device manufacturers have become frustrated over having to comply with either conflicting or redundant marketing requirements. Communications between countries with medical device programs have also been hampered as a result of differing regulatory processes and nomenclature.

As these difficulties have grown, it became apparent that harmonizing device regulatory requirements on an international level was imperative. This realization served as the catalyst to the formation of a Global Harmonization Task Force (GHTF) in the early 1990's, which is endeavoring to unify international regulatory requirements pertaining to quality systems and audits, premarket evaluation and post-market vigilance and surveillance. PAHO/WHO Member States that decide to embark upon medical device programs are encouraged to heed the

work outputs of the GHTF in order to profit from the experiences of its participant nations and thereby avoid further proliferation of disparate regulatory regimes for medical devices.

B. ESSENTIAL FEATURES

With any new undertaking, certain basics are critical to success. In existing device regulatory systems, there are, indisputably, features common to them. All must be considered by governments interested in regulating medical devices. A prerequisite to any program is the adoption of a clear legal definition of the term “medical device” in order to distinguish this commodity from others that are also subject to regulation (e.g., pharmaceuticals). In terms of an actual program structure, the features can be grouped into four basic categories. The first two activities can apply to importer countries as well as those with native medical device industries. The latter two apply chiefly to countries with domestic producers of medical devices.

1. Establishment of a ***procedure for identifying manufacturers*** (and others) with business operations in the country for which the regulatory program is being devised, as well as for imported and domestically-produced products distributed within national borders. This element should also encompass information on a product’s history to guard against unscrupulous marketers of previously-used devices that are intrinsically defective, have outlived their normal life expectancies and/or have been inadequately reconditioned for re-sale.
2. Initiation of a system to ***maintain vigilance over marketed products*** to ensure their continued safety and quality, as well as ongoing regulatory compliance by manufacturers after obtaining market clearance. As an adjunct, a method for information sharing among users and national health authorities of similar devices is vital to preventing additional adverse incidents and their unwanted health effects.
3. Implementation of a ***broad-based, regularized program of manufacturing site inspections and audits*** to verify corporate conformance with clearly-defined manufacturing standards and methods for validating quality assurance in commercial production of devices.
4. Construction of a regulatory system that is risk-based: that is, a ***system that stratifies and applies premarket assessment controls based on the risk (or hazard) potential*** of a product, as well as the potential for misuse and the breadth of commercial distribution, known or projected.

SECTION II

A Modular Approach To A Regulatory Program For Medical Devices

A. PROGRAM OVERVIEW

Medical Device Definition

A rudimentary step in establishing a device regulatory system is to clearly define what is meant by the term “medical device” and to differentiate it from other products for which a government body may have regulatory oversight responsibilities. “Medical device” is used by many as an all-encompassing term that refers to medical technology, medical supplies and medical equipment. The distinctions between each of these terms is probably less critical than demarcating devices from drugs. Fundamentally, the difference lies in the mechanism of action.

In the case of drugs, the product generally is metabolized by the body for some intended effect. In contrast, devices generally depend on physical interaction (i.e., mechanical, thermal, electrical or other form of non-metabolic action) to achieve a desired effect.

Devices differ from drugs in other respects not directly relevant to the issue of legal definition. For example, many devices have a considerably shorter useful life than drugs given the high degree of innovation and constant turnover due to technological obsolescence. Unlike the drug industry, which (other than biotechnology) remains relatively static, the device industry is a dynamic one, with a diversity of products that is unparalleled in comparison to the field of pharmaceuticals. In turn, this diversity leads to spirited entrepreneurialism, particularly among small businesses. Thus the composition of the drug industry vis-a-vis the device industry is vastly different. Because the make-up of the device industry is far more heterogeneous, with a large proportion of small companies, special challenges face those tasked with regulating these products.

Generally speaking, devices can also have considerably higher initial procurement costs. Purchasers face the added cost of maintenance of non-disposable devices over their lifespan that can extend for years. A final difference is that devices are used by a complex network of health professionals, ancillary health care workers and consumers, whereas drugs are generally prescribed by doctors, dispensed by pharmacists and self-administered by patients.

These practical distinctions can affect the crafting of a legal definition. Thus it is suggested that a medical device be thought of as an instrument, apparatus, machine, implant or in-vitro reagent whose use is intended for the diagnosis of disease, or for the cure, mitigation, treatment or prevention of disease, or for affecting the structure or function of the body for some medical purpose. If a country’s legal system differentiates devices from drugs, the definition should

also specify that devices do not achieve any of their intended purposes by means of chemical action within or on humans and are not dependent on being metabolized to achieve a result.

It should be recognized that the line distinguishing drugs and devices can sometimes be blurred as discrete products are physically, chemically or otherwise combined to form a single product or packaged together in order to achieve a particular clinical outcome. Medicated wound dressings, bone cements with antibiotics, syringes pre-filled with specific drugs, inhalers for administering aerosolized drugs and dental composites with fluoride are but a few examples.

Particularly in cases when a government has vested oversight responsibilities for pharmaceuticals, biologicals and medical devices in different organizational units, questions can arise as to how the finished combination product will be regulated and by which government entity. Answering these questions can be based on the primary mode of action of the finished product. This in turn can be determined by categorizing the combination product in the same way as other countries that have already cleared the product, or by requiring manufacturers, importers or others seeking market clearance to provide information that describes: (1) the product and its known modes of action; (2) the product's components and their individual composition; (3) the manufacturing processes used; (4) proposed use indications and schedule/duration of use; and (5) dosage and route of administration.

Market Entry Notification

Overall, a critical baseline requirement of any medical device program, irrespective of its complexity, is the acquisition of information about the establishment seeking to commercially distribute a product. Equally important is the availability of information—particularly for imported devices that may be second or later generation products which have been refurbished—describing the performance history of the product and any individual adverse events or performance trends associated with its use. These dual objectives can be accomplished by requiring manufacturers of devices to submit premarket notifications to the national regulatory body.

One of the main elements of a notification process is the identification of the establishment seeking to sell or otherwise conduct business within a national jurisdiction (often referred to as “registration” or “notification”), in addition to the identification (or “listing”) of the products to be marketed in that jurisdiction. (This is also sometimes referred to as registration, particularly as it applies to pharmaceuticals.)

Up-to-date records on the identity and physical location of manufacturers, importers and distributors (and perhaps other entities, such as refurbishers and contract sterilizers), and on their products and site(s) of manufacture enable government health officials to locate device establishments in the event some difficulty arises once the product is in commercial use. This is especially crucial in emergency situations when, for example, circumstances involving a defective device require market removal, product correction and/or health alerts to users. With this information readily available, governments need to also perform periodic inspections and spot checks to ensure ongoing compliance by indigenous producers of medical devices.

Countries that rely on imports as their primary or exclusive source of medical equipment are also strongly advised to have in place a program that assures that the necessary steps have been taken to insure device safety, quality and effectiveness. Some countries require businesses seeking market clearance to provide descriptive information relating to their clinical performance, past and present. Requiring this information as a prerequisite to marketing can be a great asset to government officials entrusted with public health and welfare and/or the responsibility of procuring medical equipment. Information on patient morbidity and mortality, attributable to the performance of medical devices, as well as regulatory actions taken by other regulatory bodies as a result of device failures, can better ensure well-informed decisions before devices are allowed entry into a national jurisdiction.

A pragmatic variance on this approach is for an importing country to rely solely on the market approval granted by countries with comprehensive regulatory systems. While this can simplify the process, it also places increasingly heavy burdens on the countries where approval was initially obtained in terms of producing export certificates or verifying representations made by product importers. It can also diminish the amount of self-control that an importing country exercises over the safety and quality of devices crossing its borders.

Countries that require this information may also want to insist that establishments submit annual update notifications as a means for government officials to monitor the commercial status of businesses operating in their countries, the volume of devices distributed and how well the products are performing. That is, have the products caused or been linked to patient deaths, injuries or illnesses? As is customary in some countries, the administrative costs of this notification activity can be borne by applicants to offset a portion or all of the costs associated with processing of notifications and storage and maintenance of official records. (Other cost-recovery mechanisms are possible.)

Post-Market Vigilance

No amount of rigor in any premarketing review process can predict all possible device failures or problems arising from product misuse. Thus, the ability to monitor the performance of marketed devices is an essential component of a device regulatory system. How elaborate a system is for tracking device performance, documenting problems and imparting vital information about device-related incidents with other users is, of course, a function of available resources and perhaps other local and national considerations.

It is recommended, however, that some surveillance activity be initiated. This can range from routine gathering of information related to the performance of individual devices (as well as trend data for generic types of devices) collected by other government or private organizations to some form of documenting system—mandatory or voluntary—that is operated by the regulatory body. Combined with establishment and product information obtained via a premarket notification procedure, post-market vigilance data can be invaluable in pinpointing problems and achieving prompt remediation.

Manufacturing Controls, Inspections Audits and Safety and Efficacy/Performance Assessment

The final two levels of a device regulatory program, perhaps more than any other, are ones that must be adapted to the socioeconomic conditions, infrastructural capacities and unique needs of individual countries. There is a broad spectrum of available mechanisms for regulating product safety, which can be selectively adopted, incrementally applied, or instituted en bloc. This menu of regulatory controls gives countries broad discretion in designing systems that are best suited for them and the constituencies they represent.

Whichever route a country chooses, it is strongly suggested that some form of graduated regulation be employed. This can be done using hierarchical, risk-based regulation, in a manner similar to the processes used by the United States, European Union and others. Alternatively, products can be typecast and arrayed by generic category, e.g., implantable, invasive, non-invasive, electrical, life-supporting, etc. Regardless of the regulatory route chosen, careful consideration should be given to the sub-elements that will constitute the operational basis for

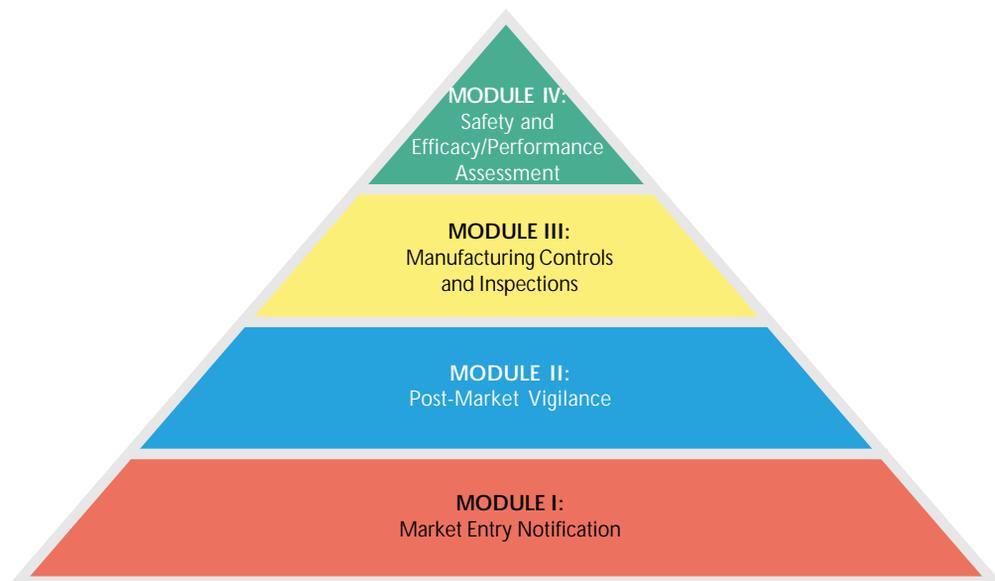
assessing device safety and efficacy (the term “effectiveness” is also used synonymously in this text). These can include:

- site inspection of manufacturing facilities and the practices used in mass production of medical devices;
- required manufacturer conformance with national or international consensus standards developed by third parties that address product safety, quality, effectiveness, performance and sterility of finished devices;
- premarket testing of production devices, either by the regulatory body, or the manufacturer or an independent testing entity, that demonstrates conformance with applicable standards and other performance and marketing requirements;
- mandatory premarket evaluation of new devices and market clearance to attest that safety, effectiveness and performance requirements are met;
- controls under which devices can be marketed: that is, specifications on the conditions under which devices can be offered for sale, in addition to who may use particular devices and under what conditions.

B. SPECIFIC PROGRAM COMPONENTS

Recognizing that no regulatory model is wholly adaptable to every situation, this section offers a broad and more detailed presentation of the critical elements of a device regulatory program, as summarized previously. The main elements and specific requirements are presented in a modular format and color-coded to assist readers in locating the text that corresponds to each of the colored modules shown on the next page. Modularizing the program is intended to enable countries to adopt as little or as much as their individual situations dictate.

This flexibility is purposefully offered in light of the fact that some countries have few or no device producers within their jurisdiction and thus rely on importation as the principal means for acquiring medical products. Under this scenario, more limited requirements may be appropriate. On the other hand, countries with device manufacturers conducting business operations within their geographical borders may require a more extensive regime of regulatory controls. Some overlap is unavoidable since the suggested regulatory paradigm is pyramidal (as depicted later), meaning that some baseline requirements may be common to both scenarios. Also, depending upon a country’s own needs, requirements can be integrated: that is, features from one module can be combined with those of another module without, necessarily, the full adoption of both.



Module I

Market Entry Notification

As discussed previously, one of the entry-level steps in building a medical device regulatory program should be establishment registration, product listing and summary information on product performance, collectively referred to as notification. (A sample notification form is provided on pages 18-19.) This minimalist approach can be carried out on either a voluntary or mandatory basis, although requiring the submission of such baseline information will provide a higher degree of assurance of comprehensive and usable records.

In the case of notification, this requirement can be applied to a number of different types of establishments that throughout the course of device production and distribution can have an impact on the finished product. As a practical matter, it can be accomplished with relative ease and a minimum of paperwork, although storage of data should be accomplished, if practicable, using a computerized database. When employing the premarket notification method, it is suggested that the name of establishment, location (including multiple sites) and identity of an authorized contact person and type of business establishment be identified. This requirement should apply to a:

- **manufacturer** (person or business that produces an article that meets the legal definition of medical device);

- **distributor**, including multiple distributors of the same device (person or business that receives finished devices from another establishment for the purpose of offering them for commercial sale);
- **importer** (person or business that receives devices from foreign manufacturers for the purpose of offering them for commercial sale and/or distribution in the recipient country);
- **repackager** (person or business that packages finished devices from bulk or repackages devices made for shipment in multiple containers);
- **relabeler** (person or business that changes the content of product labeling offered by the original manufacturer for distribution under its own name);
- **contract sterilizer** (person or business that provides sterilization services for another establishment's devices); and
- **refurbisher/remarketer** (person or business that assumes ownership of previously-used devices and reconditions them for re-sale).

In addition, applicants should be required to provide basic information about the products intended to be sold and distributed. One approach is to group products into three clusters: **active implantables** (such as cardiac pacemakers and implantable infusion pumps); **general medical devices** (such as wheelchairs, scalpels and bandages); and **in-vitro diagnostics**, which could include tests kits for hepatitis, pregnancy, HIV, etc. Because applicants may have multiple manufacturing locations, it is also advised for purposes of traceability to have the site of manufacture for a particular product identified in the notification.

Notification forms should provide instructions as to where registrants should direct the information. Countries may also wish to specify timeframes for filing notifications as a prerequisite for an establishment to initiate operations (for example, 30 to 60 days prior to commencing a business or commercial activity).

S A M P L E

MARKET ENTRY NOTIFICATION
(To be completed by domestic or foreign establishment)
[INSERT NAME/ADDRESS OF DEVICE IMPORTER COUNTRY]

SECTION A

ESTABLISHMENT NAME:

ESTABLISHMENT LOCATION (Street Address):

CITY:

COUNTRY:

ZIP CODE/POSTAL ADDRESS:

AUTHORIZED ESTABLISHMENT CONTACT/POSITION TITLE:

TELEPHONE No.:

FAX No.:

E-MAIL ADDRESS:

ESTABLISHMENT TYPE (Check one):

- | | |
|--|---|
| <input type="checkbox"/> ORIGINAL EQUIPMENT MANUFACTURER | <input type="checkbox"/> REPACKAGER/RELABELER |
| <input type="checkbox"/> REFURBISHER/REMARKETER | <input type="checkbox"/> CONTRACT STERILIZER |
| <input type="checkbox"/> DISTRIBUTOR | <input type="checkbox"/> IMPORTER |

SECTION B

PRODUCT TYPE (Check one):

SITE OF MANUFACTURE:

- ACTIVE IMPLANTABLE
 GENERAL MEDICAL DEVICE
 IN VITRO DIAGNOSTIC

DEVICE IDENTIFICATION (Give name, number, other relevant identifier information):

SECTION C

PRODUCT APPROVAL STATUS (Check more than one if applicable):

OFFICIAL USE ONLY

- APPROVED BY US FDA
 APPROVED BY EUROPEAN AUTHORITY (CE MARK)
 APPROVED BY [specify nation(s)]: _____

APPLICANT ID No.: _____

DATE OF RECEIPT: _____

DATE OF APPROVAL/DISAPPROVAL: _____

SECTION D

PRODUCT HISTORY:

HAS THE PRODUCT TO BE SOLD BEEN SUBJECT OF REGULATORY IN THIS OR ANOTHER COUNTRY IN THE LAST YEAR? (IF YES, IDENTIFY COUNTRY)
Yes _____ No _____

HAS THE PRODUCT TO BE SOLD EVER BEEN THE SUBJECT OF A VOLUNTARY MARKET WITHDRAWAL IN THIS OR ANOTHER COUNTRY? (IF YES, IDENTIFY COUNTRY) Yes _____ No _____

HAS THE PRODUCT TO BE SOLD EVER BEEN THE SUBJECT OF A HEALTH ADVISORY? Yes _____ No _____

PROVIDE A SUMMARY REPORT ON THE PERFORMANCE HISTORY OF THE DEVICE TO BE SOLD (INCLUDE DESCRIPTION OF ANY ADVERSE EVENTS ATTRIBUTED TO THE PRODUCT THAT RESULTED IN COMPLAINTS RECEIVED BY YOUR ESTABLISHMENT FROM USERS AND RELATED REPORTS MADE TO NATIONAL GOVERNMENTS

- NO PROBLEMS REPORTED
- PROBLEM(S) REPORTED (SPECIFY NATURE OF PROBLEM(S) AND NUMBER OF ADVERSE REPORTS; ATTACH SUPPLEMENTAL INFORMATION IF AVAILABLE ON BASELINE DATA FOR PRODUCT SOLD/DISTRIBUTE):

IS THE PRODUCT AN IMPLANTABLE? Yes _____ No _____

HAS THE PRODUCT BEEN EXPLANTED AND RE-CONDITIONED FOR SALE? Yes _____ No _____

IF KNOWN, SPECIFY REMAINING PRODUCT LIFE EXPECTANCY: MONTHS _____ YEARS _____

IF YOU ANSWERED "YES" TO EITHER OF THE PREVIOUS TWO QUESTIONS, ANSWER THE FOLLOWING:

HAS THE PRODUCT BEEN INDEPENDENTLY TESTED FOR CONFORMANCE WITH SAFETY/QUALITY SPECIFICATIONS? Yes _____ No _____

IS THE MANUFACTURING PROCESS IN COMPLIANCE WITH GOOD MANUFACTURING PRACTICES AND/OR ISO 9001 STANDARDS?
Yes _____ No _____

SECTION E

I HEREBY CERTIFY THAT THE FOREGOING INFORMATION IS COMPLETE AND FACTUAL. I UNDERSTAND THAT FAILURE TO REPORT ALL REQUIRED INFORMATION OR SUBMISSION OF FALSE OR MISLEADING INFORMATION IS A CRIMINAL VIOLATION, PUNISHABLE BY FINE OR IMPRISONMENT OR BOTH.

SIGNATURE OF AUTHORIZED ESTABLISHMENT OFFICIAL

DATE

Module II

Post-Market Vigilance

For detailed guidance in this area, it is suggested that readers refer to the following documents prepared and endorsed by the Global Harmonization Task Force (GHTF), an international consortium of device regulators and manufacturers whose mission is to develop uniform regulatory approaches for use by national competent authorities.

- **Minimum Data Set for Manufacturer Reports to the National Competent Authority**
- **Guidance on How to Handle Information Concerning Vigilance Reporting Related to Medical Devices**
- **Global Medical Devices Vigilance Report**
- **National Competent Authority Report Criteria**
- **Manufacturer Trend Reporting on Post-Market Medical Device Associated Adverse Events**
- **Adverse Event Reporting Guidance for the Medical Device Manufacturer Or Its Authorized Representative**

These documents can be obtained by visiting the GHTF Internet Web site: **www.ghtf.org**. Once you have accessed the Home Page, click on “GHTF Documents” and then select “Study Group 2 - Medical Device Vigilance/Post-Market Surveillance.” The documents listed above can be found in this category. Additional guidance in this area is expected in the future.

Please note that reference to or use of this material does not represent endorsement of the Pan American Health Organization or the World Health Organization.

Module III

Manufacturing Controls and Inspections

For detailed guidance in this area, it is suggested that readers refer to the following documents prepared and endorsed by the Global Harmonization Task Force (GHTF), an international consortium of medical device regulators and manufacturers whose mission is to develop uniform regulatory approaches for use by national competent authorities.

- **Guidance on Quality Systems for the Design and Manufacture of Medical Devices**
- **Design Control Guidance for Medical Device Manufacturers**
- **Process Validation Guidance for Medical Device Manufacturers**
- **Guidelines for Regulatory Auditing of Quality Systems of Medical Device Manufacturers: Part 1 - General Requirements**
- **Audit Language Requirements**
- **Training Requirements for Auditors**

These documents can be obtained by visiting the GHTF Internet Web site: www.ghtf.org. Once you have accessed the Home Page, click on “GHTF Documents” and then select “Study Group 3 - Quality System Requirements & Guidance” and “Study Group 4 - Auditing.” The documents listed above can be found in these two categories. Additional guidance in these areas is expected in the future.

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Module IV

Safety, Efficacy and Performance Assessment

Introduction

Several of the world’s existing device regulatory systems require manufacturers to prove the safety, effectiveness and/or performance of their products as a condition to commercial marketing, in addition to having sufficient information to guide doctors on the appropriate use of the products. While the standards of proof may vary from one regulatory system to another, and depending on whether governmental entities or non-government entities should bear primary responsibility for conducting premarket evaluations, there is general consensus on the value of having medical treatment theories and technological concepts validated by controlled scientific experiments before wide-scale use in humans.

One of the foremost decisions a regulatory authority must make in establishing a premarket review program is whether the program should be oriented strictly to product safety or whether demonstration of clinical effectiveness/performance should also be a prerequisite to marketing. Under a “safety only” system, a regulatory authority would presumably evaluate safety data for a new device derived

from laboratory studies. If such studies, for example, show that a device is safe and can perform its purported medical functions, it would be allowed on the market. (Some countries treat the efficacy decision as a part of their health care financing arrangements.)

Under a “safety only” system, device effectiveness would be measured after marketing occurs through a process of gradual consensus based on accumulated experience with the product by health professionals and consumers, as well as evaluations in the medical literature. Under such a program, ineffective devices would presumably lose their standing in the marketplace, demand would diminish and, ultimately, the product would cease to be manufactured.

Another school of thought is that device safety is inextricably linked to effectiveness/performance. Since few if any medical devices are absolutely safe, making safety judgments involves a benefit-risk decision. In other words, one cannot ask simply whether a product is safe, but rather whether it is safe enough in view of the benefits to patients. For example, the benefit of a life-saving device where no alternative treatment options exist, may outweigh known risks. On the other hand, the use of a device with minimal benefits might not be justified unless the corresponding risks are low and well understood.

Admittedly, assessing effectiveness can be a more time-consuming and costly endeavor. In recent years, the complexity of medical technology and the rising demand for cost-effectiveness information have contributed to the ever-growing need for clinical trials as an objective method of scientific inquiry. However, measuring patient benefits is not an easy undertaking since some patients may benefit from a particular medical device while others do not. Thus it becomes important for health care providers who use a device to know what groups of patients will benefit from it and under what circumstances. Comparison of a particular device with other available forms of treatment enables health practitioners to make rational decisions about patient management.

Relying on post-market consensus-building to gauge a product’s effectiveness can have an impact on patient care in two ways. First, before consensus is reached among health professionals, a significant number of patients may receive relatively ineffective and potentially dangerous treatments from unproven devices. In such cases, patients could be deprived of more effective therapies and scarce health care resources may be expended for ineffective or marginally effective medical procedures, which exacerbates the resource problem. Second, the data to establish a consensus may be inadequate, particularly if it comes from practitioners’ personal experiences. Individual clinicians rarely treat patients in sufficient numbers and under controlled conditions to be able to detect and measure adverse effects or assess clinical outcomes among large patient populations.

Assessing Device Safety, Efficacy and Performance

For detailed guidance in this area, it is suggested that readers refer to the following document prepared and endorsed by the Global Harmonization Task Force (GHTF), an international consortium of medical device regulators and manufacturers, whose mission is to develop uniform regulatory approaches for use by national competent authorities.

Three documents, relevant to this program area, have received endorsement from the GHTF. They are:

- **Essential Principles of Safety and Performance of Medical Devices**
- **Labelling for Medical Devices**
- **Role of Standards In the Assessment of Medical Devices**

These documents can be obtained by visiting the GHTF Internet Web site: www.ghtf.org. Once you have accessed the Home Page, click on “GHTF Documents” and then select “Study Group 1 - Regulatory Requirements/Premarket Review.” The documents listed above can be found in this category. Additional guidance in this area is expected in the future.

Please note that reference to or use of this material does not represent endorsement of the Pan American Health Organization or the World Health Organization.

The Principles of Quality Clinical Studies

Should a regulatory authority decide to compel domestic manufacturers to show evidence of the safety, effectiveness and/or performance of medical devices, a basic understanding of what constitutes quality clinical trials is essential. The principles of good clinical study design encompass a wide range of considerations. Among these are the statistical power of a study, number of human subjects enrolled in the study, protections for study subjects, clearly defined study objectives and endpoints, and controls against bias and error. In a stepwise fashion, the following generally describes the key elements of a quality clinical trial.

- A study protocol should state a clear purpose: that is, a hypothesis to be tested. This is usually phrased as a research question to address the medical claims being made for the device.
- If the claims for a product are inadequately known or defined, a sponsor may wish to conduct a pilot or feasibility study on a small population of patients. This step will allow claims to be identified more clearly; study

procedures to be validated; estimates of patient outcomes and variables that can affect the larger study to be obtained; and safety and effectiveness endpoints (e.g., patient inclusion/exclusion criteria) to be defined.

- A study design should be capable of testing the stated hypothesis. This means that issues such as what constitutes success and failure as they relate to specific study endpoints must be addressed. There must also be an appropriate control group for comparison and a sample size large enough to answer the major questions specified in the protocol.
- The study design must also include proper methods to measure the defined endpoints. Comparability is the goal and can be achieved through such techniques as randomization and masking (or blinding), in addition to efforts to ensure as close to 100 percent patient follow-up as possible in both study and control groups.
- Finally, a study protocol should identify the methods of data analysis that will be used (i.e., statistical tests), and explain any plans to exclude certain patients from the analyses, any planned sub-group comparisons, or “pooling” of the data, and which of several endpoints (if applicable) will be the primary one.

The principles that govern human subjects protection today are found in the Nuremberg Code, Declaration of Helsinki and Belmont Document, which are provided in the Appendix (see page 43).

The Nuremberg Code was developed in the late 1940's for the Nuremberg military tribunal as standards by which to judge human experimentation. The Code captures many of what are now relied upon as the basic principles for the ethical conduct of research involving human subjects: voluntary consent, minimization of risk and harm, favorable risk-to-benefit ratio, qualified researchers using appropriate research design and freedom of the subject to withdraw at any time.

The Declaration of Helsinki, prepared by the World Medical Association in 1964 and revised in 1975 and 1989, embraces principles similar to those in the Nuremberg Code. It distinguishes therapeutic from non-therapeutic research and recommends that:

- clinical research be conducted in accordance with accepted scientific methodologies;
- research objectives are balanced against possible risks to subjects; and
- patients enrolled in clinical trials are made fully aware of the risks and benefits of the procedure and are afforded the opportunity to give informed consent.

The Belmont Document was published by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in 1979. This document identifies three essential requirements for the ethical conduct of research involving human subjects:

- **respect for persons:** recognition of the personal dignity and autonomy of individuals and special protection for those persons with diminished autonomy;
- **beneficence:** an obligation to protect persons from harm by maximizing anticipated benefits and minimizing possible risks of harm; and
- **justice:** fairness in distribution of burdens and benefits, often expressed in terms of treating persons of similar circumstances or characteristics similarly.

C. LEGISLATIVE MODEL

On the assumption that countries without regulatory controls for medical devices lack the basic authorizing legislation upon which to construct a program, this section provides a template for use by health agencies and legislative bodies.

Section 1

Definitions

- (A) “Product” means any medical device, medical equipment, medical technology or medical product.
- (B) “Medical product” or “medical device” means any article intended for use in, or actually used in, the diagnosis, treatment or prevention of disease or other health condition in humans by a health professional or a patient/consumer.
- (C) “Investigational product” means a product that is experimental and has not yet been accepted for marketing.
- (D) (1) “Safety” means the benefit of a product to a patient who is medically diagnosed or treated with the product outweighs the risk that the product might cause harm to the patient.

- (2) “Effectiveness” or “efficacy” means a product can be shown by valid scientific evidence to produce an intended clinical effect in a target population.
- (3) “Performance” means a product performs as intended and in accordance with associated labeling and is in conformance with applicable technical specifications and relevant product standards.
- (E) “Person” means individual, partnership, corporation, association, organization or health professional.
- (F) “Health professional” means any physician, pharmacist, nurse or any other person who delivers health care.
- (G) “Facility” means any factory, warehouse, store, pharmacy, hospital, carrier, vessel or any other place where products are manufactured, processed, imported, packed, refurbished, held, distributed, dispensed or sold.

Section 2

General Requirements

- (A) A person (including any manufacturer, importer, distributor or refurbisher) shall not sell any product that is not safe, effective, properly labeled and in compliance with applicable registration or market approval requirements, or that otherwise violates the requirements of this law or the regulations issued under it.
- (B) A manufacturer, importer, distributor, repackager/relabeler or refurbisher/remarketer shall register with the regulatory control authority and shall submit a list of products for which they are responsible. Registration and listing information shall be periodically updated as required by the regulatory control authority. Medical products shall be listed under standardized nomenclature as required by the regulatory control authority.
- (C) A person shall submit all required applications, documents and other information and shall document any voluntary recalls or other corrective action(s) involving the product to the regulatory control authority.
- (D) Any person, other than consumer-patients, who becomes aware that a medical device may have caused or contributed to an adverse event shall evaluate the information submitted and shall document the event concurrently to the manufacturer and the regulatory authority.

- (E) Any manufacturer, importer, distributor or other business entity covered by this legislation shall establish a procedure for handling device-related complaints from users, as well as for documenting device-related events to the regulatory control authority.
- (F) A person shall not provide any false or misleading information:
 - (1) to the regulatory authority in applications, documents or other information;
 - (2) in labeling, advertising or other information about a medical device manufactured, imported, distributed or otherwise commercialized, or used in medical practice by that person.
- (G) A person in a facility shall permit an inspection by the regulatory authority, its officers and its employees.
- (H) A person shall establish and maintain all records pertaining to medical devices that are required by this law or the regulatory control authority, and shall make such records available to the regulatory control authority upon request.

Section 3

Post-Market Vigilance for Approved Medical Devices

- (A) In addition to complying with all other requirements, manufacturers/ sponsors of approved medical devices shall comply with whatever requirements the regulatory control authority may impose at the time market approval is granted or at any time thereafter, including:
 - (1) the conduct of additional tests or studies, with acceptable results;
 - (2) the limitation of a device to prescription use or to other restricted use;
 - (3) the tracking of a medical device to facilitate product correction or market removal in the event of a malfunction or other device failure to which an adverse impact on human health can be attributed; and
 - (4) the conduct of post-market surveillance to monitor the performance of a device in actual use, particularly in cases where long-term performance could not feasibly be demonstrated during the premarket testing stage.

Section 4

Surveillance by Regulatory Control Authority

The regulatory control authority may through its officers and employees:

- (1) conduct investigations of persons and medical devices, including inspections;
- (2) enter a facility for the purpose of inspecting the facility, physical records and any other materials in the possession of a person who manufactures, distributes, holds or sells medical devices, and may take photographs, gather physical evidence and collect product samples;
- (3) issue an order requiring that a manufacturer, importer or other business entity responsible for medical devices submit the results of product safety and effectiveness testing and, absent such testing, issue an order requiring that such tests be performed and the results submitted to the regulatory control authority; and
- (4) inspect and copy all records, regardless of their location, that pertain to medical devices and a facility's compliance with applicable laws and regulations.

Section 5

Requirements for Medical Device Manufacturing and Quality Assurance

- (A) A manufacturer, processor or packer shall manufacture all medical devices in conformance with good manufacturing practices and shall not commercially distribute any device that has not been produced in conformity with such requirements.
- (B) A manufacturer, processor or packer shall assure that all medical devices meet all requisite specifications and product standards prior to offering them for sale.
- (C) A manufacturer, processor or packer shall establish and maintain records pertaining to all manufacturing, processing and packing activities, as well as product distribution by lot number.
- (D) A person shall not distribute any medical device that is unapproved or which has a biological, chemical or physical property that may cause an unacceptable human health risk.

- (E) A person shall not distribute any medical device that is not labeled with the identity of the product and, if appropriate, its ingredients, the name and address of the manufacturer/sponsor, all indications relating to use of the device, all relevant warnings, precautions and contraindications, and such other information as required by the regulatory control authority.
- (F) A person shall not distribute any medical device if the product labeling or advertising is false or misleading.

Section 6

Premarket Evaluation Requirements

- (A) Before offering a new medical device for sale, the manufacturer/sponsor shall submit an application to the regulatory control authority or a surrogate accredited review entity, and obtain market approval from the authority or accredited review entity before any sale can occur. To ensure an unbiased, objective and qualified review, the authority will assign review responsibility for an application to scientists, clinical experts and/or other officials who do not have any conflict of interest concerning the medical device.
- (B) The regulatory control authority may establish different investigational and premarket requirements based upon the complexity and risk of the medical device.
 - (1) To assure that the scientific and clinical investigations performed by the manufacturer/sponsor are appropriate to enable a decision by the regulatory control authority or review entity on a medical device, it is imperative that the authority elucidate in its instructions to manufacturers/sponsors what information is required in premarket applications.
 - (2) The regulatory control authority or accredited review entity shall use whatever means of communicating premarket application requirements to manufacturers/sponsors are deemed to be the most effective and appropriate. These can include regulations, guidelines, policies, points-to-consider documents, presentations at industry meetings and consultative discussions between the authority and manufacturers/sponsors about individual medical devices.
- (C) During the investigational phase of product development, the regulatory control authority or accredited review entity may vary the requirements for different types of medical devices and will permit researchers and manufacturers/sponsors the flexibility to develop new devices provided that human subjects are adequately protected.

- (D) The manufacturer/sponsor shall collect information for the premarket application during the investigational phase.
- (E) Premarket testing can encompass the following: physical and animal tests, non-clinical laboratory studies and clinical trials.
- (F) Manufacturers/sponsors shall conduct investigational tests in accordance with scientifically sound protocols and procedures, in addition to good laboratory practices (GLPs) in the case of non-clinical laboratory studies.
- (G) With respect to clinical research, the manufacturer/sponsor shall inform all human subjects that the medical device being tested is investigational and the nature of the risks involved with its use, obtain patients' written consent prior to the medical procedure and have safeguards that are in accordance with the Declaration of Helsinki and other international accords to protect human subjects.
- (H) The manufacturer/sponsor is responsible for and shall assure that all information and data generated from investigational studies are accurate, comprehensive and thoroughly analyzed.
- (I) The manufacturer/sponsor shall submit a premarket application to the regulatory control authority or another entity duly authorized by the regulatory control authority that includes all relevant data from preclinical laboratory, animal and clinical research, in addition to proposed product labeling that includes clinical indications, directions for use, warnings, precautions and contraindications and/or demonstration of conformance with applicable product standards.
- (J) The regulatory control authority and all accredited review entities shall have procedures to evaluate the safety, effectiveness and quality of new medical devices as a condition to granting market approval to a manufacturer/sponsor.
- (K) The manufacturer/sponsor bears the burden of proof in the premarket application to demonstrate to the regulatory control authority or an accredited review entity that a medical device is safe and effective, is manufactured in accordance with quality standards and its benefits outweigh the risks associated with its use.
- (L) The regulatory control authority or accredited review entity will determine within a specified period of time whether to grant market approval to the manufacturer/sponsor who submits a premarket application.
- (M) Upon completion of its review of a premarket application, the regulatory control authority or accredited review entity shall notify the manufacturer/sponsor of its decision with respect to:
 - (1) market approval, in addition to any marketing conditions; or

- (2) denial of market approval, the basis for the decision and the procedures the manufacturer/sponsor may follow to appeal the decision of the regulatory control authority or surrogate review entity.
- (N) In addition to other requirements, the manufacturer/sponsor of any medical device subject to approval shall comply with such additional requirements that apply to the product which the regulatory control authority may deem necessary.

Section 7

Emergency Orders By Regulatory Control Authority Inspectors

- (A) If during an inspection of a facility, a regulatory control authority inspector observes a violation that involves a failure on the part of the manufacturer/sponsor or other business entity to obtain market approval, or involves a product that poses a risk of harm to health, or a serious violation of good manufacturing practices, or is otherwise a serious violation of applicable laws and regulations, the inspector is authorized to order one or more of the following actions:
 - (1) shutdown of the facility;
 - (2) detention of medical device(s);
 - (3) physical destruction of medical device(s);
 - (4) termination of all shipments of medical devices until the regulatory control authority reauthorizes distribution.
- (B) An emergency order by an inspector shall be approved by a supervisor within a specified period of time and shall remain in effect for a specified period of time pending further action as described in Section 8.

Section 8

Enforcement of Requirements

- (A) The regulatory control authority is authorized to initiate the following actions against persons or medical devices:
 - (1) detention or seizure of the medical device(s);
 - (2) physical destruction of the medical device(s);
 - (3) recall of the medical device(s);

- (4) ordering of the responsible person to perform corrective actions in order to bring the medical device(s) into conformity with applicable laws and regulations, including the provision of new or remedial parts to all customers or users of the product;
 - (5) banning of the medical device(s) if it/they cannot be corrected in a manner that insures product safety and effectiveness;
 - (6) dissemination of a public warning to health professionals, consumers/patients or other users of the medical device(s).
 - (7) ordering a change in the medical device(s), including its/their manufacturing methods, labeling, advertising or use.
- (B) Following initiation of any or all of the actions specified in (B), the person responsible for the medical device(s) against which the order is directed shall have the right to submit written information and/or request a meeting with regulatory control authority officials to discuss the order(s) and explain why the directed actions may not be necessary.
- (C) With respect to actions against persons who violate the law and regulations:
- (1) The regulatory control authority may:
 - (a) revoke or limit the person's registration;
 - (b) initiate an administrative proceeding for civil money penalties;
 - (c) initiate a court action for criminal prosecution of the person, including any other individuals responsible for the violation; or
 - (d) debar the person, including any other individuals responsible for the violation, from future dealings with the medical devices or with the regulatory control authority.
 - (2) With respect to procedures for actions against persons, the following applies:
 - (a) Except in cases of emergency, the regulatory control authority shall first issue a warning letter to the person(s) responsible for the violation or who have control of the violative medical devices. The warning letter shall describe the violation and offer the responsible person(s) an opportunity to comply voluntarily with the law.
 - (b) Absent voluntary compliance in a timely manner and to the satisfaction of the regulatory control authority, regulatory control authority officials may initiate further action(s) against the person(s), as described below.

- (c) The person(s) against whom the action(s) is/are directed shall have the right to submit written information and/or meet with regulatory control officials to discuss the proposed actions, or request a hearing before an administrative judge if the person(s) can demonstrate the existence of a substantial issue of material fact to be presented at the hearing. If the regulatory control authority provides for a hearing, the matter shall be assigned to the administrative judge for hearing and decision.

Section 9

Regulations

- (A) The regulatory control authority may promulgate regulations on medical devices, persons or the authority's procedures in order to administer and enforce this law. Regulations may pertain to medical device safety, effectiveness, performance/quality, good manufacturing practices, good laboratory practices, premarket testing, labeling, advertising and other such matters where the regulatory control authority deems that such action is in the interest of public health protection.
- (B) With respect to procedures for issuing regulations, the following applies.
 - (1) The regulatory control authority shall offer proposed regulations to the public for comment, along with any supporting information.
 - (2) After evaluating public comments, the regulatory control authority shall issue a final regulation accompanied by an explanation of the comments and their disposition by the authority.
 - (3) In any regulation proceeding, the regulatory control authority may hold a public meeting, convene an advisory committee or use other procedures to facilitate and expand public participation and/or to improve the information that is germane to the subject of the regulation(s).

Section 10

Cooperation With Other Governments

The regulatory control authority is authorized to cooperate with other government authorities by sharing information and entering into agreements for the purpose of the safety, effectiveness and quality of medical devices and the safe use of such products.

Section 11

Public Participation

- (A) The regulatory control authority shall periodically issue a Health Register that contains the authority's proposed and final regulations, guidelines, operational policies and procedures and other information relevant to the authority's regulation of medical devices.
- (B) The regulatory control authority shall make available to the public, upon request, a copy of this law, the implementing regulations, the Health Register, a list of all registrations and the public files of all regulation proceedings.
- (C) Any member of the public may petition the regulatory control authority to issue a regulation or to initiate other action.

Section 12

Confidentiality of Information

Officers and employees of the regulatory control authority shall not make public or use for their own personal gain any trade secret or proprietary information which they obtain or become familiar with during the course of their official duties.

SECTION III

Reuse of Medical Devices

REUSE OF MEDICAL DEVICES

One of the most controversial and widely debated phenomena that has occurred during the evolution of the galaxy of medical devices has been the emergence of “single-use” (sometimes also referred to as “disposable”) devices. The onerous and time-consuming task of cleaning, repackaging and autoclaving medical devices composed of glass, metal and other durable materials has to a large degree given way to the convenience of products that can be discarded after one-time use, especially in industrialized nations of the world that are large consumers of health care goods.

But convenience has translated into increased costs to hospitals and other device user facilities, prompting many to reuse these devices several times on the same or different patients also as a means to contain costs. This may be particularly endemic in countries where medical equipment procurement resources are scarce. While anecdotal information suggests that device reuse is widespread, the actual extent of the practice and the magnitude of the risk to patients have not been firmly characterized.

This lack of information about reuse has led to questions about the inherent safety of multiple uses of single-use products. For example, are the people who reprocess disposable devices adequately trained to do so and do they conscientiously follow reprocessing methodologies and protocols, assuming any exist? Do the sterilants commonly used pose a health risk to patients and are commercially-available disinfection and germicidal agents effective for all types of plastics, ceramics and other materials used in device manufacturing—in other words, do they cause degradation of devices after multiple reprocessing cycles? Also, if devices are improperly reprocessed for reuse, are patients at increased risk of being unwittingly subjected to re-infection or cross-infection, e.g., HIV, Hepatitis-B?

Questions have also been raised as to the integrity, functional performance and clinical effectiveness of reused devices. These concerns have led many to challenge the ethics of treating patients, often without warning or consent, with reused devices that most manufacturers label and commercially distribute for single-use only. Hand in hand with the ethical considerations are issues of legal liability in terms of who bears primary responsibility for the safety and effectiveness of a product once it has been reused contrary to its single-use directions. In many legal systems, once reuse occurs, liability in part or in whole is shifted from the manufacturer of the original device to the owner or reprocessor of the reused device. Reuse of single-use devices may also invalidate product warranties.

Nevertheless, the desire for cost containment often overrides these concerns, as does word-of-mouth acceptance of the practice if it does not pose any immediate or obvious adverse health effects. A case in point is the large-scale reuse of dialyzers used in hemodialysis. There is abundant evidence of product reuse. Given the difficulty in tracing problems, such as pyrogenic reactions, to reuse can be problematic given the poor health status of the majority of dialysis patients. Indeed, some health care providers have come to accept dialyzer reuse and the trade-offs that come with it as the standard of care. While questions are persistently raised about the effects of repeated reprocessing on dialyzer membranes and their functionality compared to new dialyzers, the practice of dialyzer reuse (and reuse of ancillary equipment such as blood lines) has become increasingly popularized.

In more recent years, these concerns have spawned a rapidly-growing cottage industry of device reprocessors and refurbishers which is minimally regulated. As a result, customers essentially have no independent assurance of either the firms' business integrity or the end-safety of the devices they commercially reprocess for reuse. Thus, *caveat emptor* ("let the buyer beware") is the watchword.

Despite the rising trend in device reuse, most government regulatory authorities have not offered their approval, either tacitly or explicitly, to this practice. In fact, just the opposite is true. For example, among the nations that comprise the European Union, none has policies supporting the practice and some expressly forbid it by law. The Australian Therapeutic Goods Administration has taken a position against reuse and proposes to go a step farther by mandating informed consent prior to the use of a reprocessed device.

Historically, in the United States, the Food and Drug Administration has taken the position that the health institution or practitioner that authorizes reprocessing and reuse assumes full responsibility for product safety and effectiveness. This position has changed with FDA's publication of its Enforcement Priorities Guidance on Reuse of Single-Use Devices in August 2000. This final guidance requires premarket clearance depending on certain device risks. Thus, all reprocessors, including hospitals, will be subject to premarket requirements after a phase-in period that is to end in August 2002. Additionally, reprocessors must comply by August 2001 with certain post-market requirements including inspections, mandatory adverse event reporting, manufacturer registration, product listing, labeling, etc.

Although PAHO/WHO neither condone or disfavor reuse, both organizations recognize the economic realities faced by many Member States and the potential—real or perceived—for appreciable health care resource-savings that may accrue from this practice. At the same time, PAHO/WHO believes that as medical institutions make individual decisions about whether to reuse medical devices, consideration of possible impacts on patient safety is paramount.

In this regard, several fundamental questions must be asked.

- Is adequate medical and scientific information available to determine the safety and clinical effectiveness or specific reused disposable medical devices?
- Are there established methods for reprocessing (i.e., cleaning, disinfecting and re-sterilizing) single-use medical devices for reuse and for validating the integrity of devices reprocessed for reuse?
- What level of sterility is desired?
- What level of product function is desired or acceptable?
- Is information available to identify and exclude specific devices and/or composition materials from being reused?
- Is information available to determine the appropriate frequency and/or duration of device reuse?
- What level of surveillance of product quality is necessary to avoid product failure and prevent patient harm?
- In the absence of substantiated evidence of any health risk associated with device reuse, should health care providers be encouraged or compelled to obtain patient informed consent prior to medical treatment involving reused devices?

These are complex issues that do not lend themselves to clear cut or easy answers. Ideally, resolution is best achieved by striking a proper balance between the benefits of reuse (viewed mainly as economic) with all identifiable risks. In the end, as stated previously, the decision whether or not to reuse medical devices is one that, in most cases, cannot be made by government authorities. Rather, it is one that individual health care practitioners and/or medical institutions must make for themselves in tandem with their patients in the light of current risk-benefit and cost-benefit circumstances.

What role then should national health authorities assume with respect to advising their citizens on the appropriateness of medical device reuse? PAHO/WHO believes it is important for health authorities to keep abreast of developments, both scientific and policy, with relevance to device reuse. They should also serve as conduits through which international documents and advisories on this subject can be channeled to local health care communities. As a starting point, PAHO/WHO is presently aware of the documents listed below that address the issues of medical device reprocessing and reuse and offer them as useful references.

General Reuse

1. Association for the Advancement of Medical Instrumentation (US): “Designing, Testing and Labeling Reusable Devices for Reprocessing in Health Care Facilities - A Guide for Device Manufacturers.”
2. Association for the Advancement of Medical Instrumentation/American National Standards Institute (US): “Sterilization of Health Care Products - Requirements for Validation and Routine Control/Industrial Moist Heat Sterilization.”
3. Association for the Advancement of Medical Instrumentation/American National Standards Institute (US): “Sterilization of Health Care Products - Requirements for Validation and Routine Control/Radiation Sterilization.”
4. Canadian Healthcare Association: “The Reuse of Single-Use Medical Devices - Guidelines for Health Care Facilities.”
5. European Confederation of Medical Devices Associations: “The Case Against Reuse of Single-Use Medical Devices.”
6. Medical Devices Agency (UK): “The Reuse of Medical Devices Supplied for Single-Use Only.”
7. National Health and Medical Research Council Expert Panel on Reuse of Medical Devices Labelled As Single Use (DRAFT).
8. ECRI (US): “Special Report - Reuse of Single-Use Medical Devices: Making Informed Decisions.”
9. Food and Drug Administration (US): “Enforcement Priorities Guidance on Reuse of Single-Use Devices.”

Product-Specific

1. American Society of Gastrointestinal Endoscopy/Society of Gastroenterology Nurses and Associates (US): “Reprocessing of Flexible Gastrointestinal Endoscopes.”
2. American Society for Testing and Materials (US): “Standard Practice for Cleaning and Disinfection of Flexible Fiberoptic and Video Endoscopes Used in the Examination of the Hollow Viscera.”
3. Association for Professionals in Infection Control and Epidemiology (US); “APIC Guideline for Infection Prevention and Control in Flexible Endoscopy.”

4. International Organization for Standardization: “Retrieval and Analysis of Implantable Medical Devices.”
5. Quebec Ministry of Health (Canada): The Reuse of Single-Use Catheters.”

APPENDIX

Human Subjects Protection Guidelines and Rules

DECLARATION OF HELSINKI: RECOMMENDATION GUIDING PHYSICIANS IN BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS

Introduction

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission.

The Declaration of Geneva of the World Medical Assembly binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research, a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects.

They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. Basic Principles

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.
2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator are the sponsor, provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.
3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never on the subject of the research, even though the subject has given his or her consent.
4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.
5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.
6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Documents of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.
9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.
10. When obtaining informed consent for the research project, the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case, the informed consent should be a physician who is not engaged in the investigation and who is completely independent of this official relationship.
11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.

Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.
12. The research protocol should always contain a statement of the ethical consideration involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. Medical Research Combined With Clinical Care (Clinical Research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, re-establishing health or alleviating suffering.
2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient, including those of a control group, if any, should be assured of the best proven diagnostic and therapeutic method.
4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.
5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee.
6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. Non-Therapeutic Biomedical Research Involving Human Subjects (Non-Clinical Biomedical Research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that of that person on whom biomedical research is being carried out.
2. The subjects should be volunteers, either healthy persons or patients for whom the experimental design is not related to the patient's illness.
3. The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.
4. In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject.

THE NUREMBERG CODE

1. The voluntary consent of the human subject is absolutely essential.

This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, overreaching or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment.

The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.

2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.
3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.
4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.
5. No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur, except perhaps in those experiments where the experimental physicians also serve as subjects.
6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.
7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability or death.

8. The experiment should be conducted only by scientifically qualified persons.

The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.

9. During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seemed to him to be impossible.
10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable [sic] cause to believe, in the exercise of the good faith, superior skill and careful judgement required of him that a continuation of the experiment is likely to result in injury, disability or death to the experimental subject.

THE BELMONT REPORT

Ethical Principles and Guidelines for Research Involving Human Subjects

Scientific research has produced substantial social benefits. It has also posed some troubling ethical questions. Public attention was drawn to these questions by reported abuses of human subjects in biomedical experiments, especially during the Second World War. During the Nuremberg War Crime Trials, the Nuremberg Code was drafted as a set of standards for judging physicians and scientists who had conducted biomedical experiments on concentration camp prisoners. This Code became the prototype of many later codes¹ intended to assure that research involving human subjects would be carried out in an ethical manner.

The codes consist of rules, some general, others specific, that guide the investigators or the reviewers of research in their work. Such rules often are inadequate to cover complex situations; at times they come into conflict, and they are frequently difficult to interpret or apply. Broader ethical principles will provide a basis on which specific rules may be formulated, criticized and interpreted.

Three principles, or general prescriptive judgments, that are relevant to research involving human subjects are identified in this statement. Other principles may also be relevant. These three are comprehensive, however, and are stated at a level of generalization that should assist scientists, subjects, reviewers and interested citizens to understand the ethical issues inherent in research involving human subjects. These principles cannot always be applied so as to resolve beyond dispute particular ethical problems. The objective is to provide an analytical framework that will guide the resolution of ethical problems arising from research involving human subjects.

¹ Since 1945, various codes for the proper and responsible conduct of human experimentation in medical research have been adopted by different organizations. The best known of these codes are the Nuremberg Code of 1947, the Helsinki Declaration of 1964 (revised in 1975) and the 1971 Guidelines (codified into Federal Regulations in 1974) issued by the former U.S. Department of Health, Education, and Welfare (now the Department of Health and Human Services). Codes for the conduct of social and behavioral research have also been adopted, the best known being that of the American Psychological Association, published in 1973.

This statement consists of a distinction between research and practice, a discussion of the three basic ethical principles and remarks about the application of these principles.

A. Boundaries Between Practice and Research

It is important to distinguish between biomedical and behavioral research, on the one hand, and the practice of accepted therapy on the other, in order to know what activities ought to undergo review for the protection of human subjects of research.

The distinction between research and practice is blurred partly because both often occur together (as in research designed to evaluate a therapy) and partly because notable departures from standard practice are often called “experimental” when the terms “experimental” and “research” are not carefully defined.

For the most part, the term “practice” refers to interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success. The purpose of medical or behavioral practice is to provide “diagnosis”, preventive treatment or therapy to particular individuals.² By contrast, the term “research” designates an activity designed to test a hypothesis, permit conclusions to be drawn and thereby to develop or contribute to generalizable knowledge (expressed, for example, in theories, principles and statements of relationships). Research is usually described in a formal protocol that sets forth an objective and a set of procedures designed to reach that objective.

When a clinician departs in a significant way from standard or accepted practice, the innovation does not, in and of itself, constitute research. The fact that a procedure is “experimental,” in the sense of new, untested or different, does not automatically place it in the category of research. Radically new procedures of

²*Although practice usually involves interventions designed solely to enhance the well-being of a particular individual, interventions are sometimes applied to one individual for the enhancement of the well-being of another (e.g., blood donation, skin grafts, organ transplants) or an intervention may have the dual purpose of enhancing the well-being of a particular individual, and, at the same time, providing some benefit to others (e.g., vaccination, which protects both the person who is vaccinated and society generally). The fact that some forms of practice have elements other than immediate benefit to the individual receiving an intervention, however, should not confuse the general distinction between research and practice. Even when a procedure applied in practice may benefit some other person, it remains an intervention designed to enhance the well-being of a particular individual or groups of individuals; thus, it is practice and need not be reviewed as research.*

this description should, however, be made the object of formal research at an early stage in order to determine whether they are safe and effective. Thus, it is the responsibility of medical practice committees, for example, to insist that a major innovation be incorporated into a formal research project.³

Research and practice may be carried on together when research is designed to evaluate the safety and efficacy of a therapy. This need not cause any confusion regarding whether or not the activity requires review; the general rule is that if there is any element of research in an activity, that activity should undergo review for the protection of human subjects.

B. Basic Ethical Principles

The expression “basic ethical principles” refers to those general judgments that serve as a basic justification for the many particular ethical prescriptions and evaluations of human actions. Three basic principles, among those generally accepted in our cultural tradition, are particularly relevant to the ethics of research involving human subjects: the principles of respect for persons, beneficence and justice.

1. Respect for Persons

Respect for persons incorporates at least two ethical convictions: first, that individuals should be treated as autonomous agents; and second, that persons with diminished autonomy are entitled to protection. The principle of respect for persons thus divides into two separate moral requirements: the requirement to acknowledge autonomy and the requirement to protect those with diminished autonomy.

An autonomous person is an individual capable of deliberation about personal goals and of acting under the direction of such deliberation. To respect autonomy is to give weight to autonomous persons’ considered opinions and choices while refraining from obstructing their actions unless they are clearly detrimental to others. To show lack of respect for an autonomous agent is to repudiate that person’s considered judgments, to deny an individual the freedom to act on those considered judgments, or to withhold information necessary to make a considered judgment when, there are no compelling reasons to do so.

³Because the problems related to social experimentation may differ substantially from those of biomedical and behavioral research, the Commission specifically declines to make any policy determination regarding such research at this time. Rather, the Commission believes that the problem ought to be addressed by one of its successor bodies.

However, not every human being is capable of self-determination. The capacity for self-determination matures during an individual's life, and some individuals lose this capacity wholly or in part because of illness, mental disability or circumstances that severely restrict liberty. Respect for the immature and the incapacitated may require protecting them as they mature or while they are incapacitated.

Some persons are in need of extensive protection, even to the point of excluding them from activities which may harm them; other persons require little protection beyond making sure they undertake activities freely and with awareness of possible adverse consequences. The extent of protection afforded should depend upon the risk of harm and the likelihood of benefit. The judgment that any individual lacks autonomy should be periodically re-evaluated and will vary in different situations.

In most cases of research involving human subjects, respect for persons demands that subjects enter into the research voluntarily and with adequate information. In some situations, however, application of the principle is not obvious. The involvement of prisoners as subjects of research provides an instructive example. On the one hand, it would seem that the principle of respect for persons requires that prisoners not be deprived of the opportunity to volunteer for research. On the other hand, under prison conditions they may be subtly coerced or unduly influenced to engage in research activities for which they would not otherwise volunteer. Respect for persons would then dictate that prisoners be protected. Whether to allow prisoners to "volunteer" or to "protect" them presents a dilemma. Respecting persons, in most hard cases, is often a matter of balancing competing claims urged by the principle of respect itself.

2. Beneficence

Persons are treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well-being. Such treatment falls under the principle of beneficence. The term "beneficence" is often understood to cover acts of kindness or charity that go beyond strict obligation. In this document, beneficence is understood in a stronger sense, as an obligation. Two general rules have been formulated as complementary expressions of beneficent actions in this sense: (1) do not harm; and (2) maximize possible benefits and minimize possible harms.

The Hippocratic maxim "do no harm" has long been a fundamental principle of medical ethics. Claude Bernard extended it to the realm of research, saying that one should not injure one person regardless of the benefits that might come to others. However, even avoiding harm requires learning what is harmful; and, in the process of obtaining this information, persons may be exposed to risk of harm. Further, the Hippocratic Oath requires physicians to benefit their patients

“according to their best judgment.” Learning what will in fact benefit may require exposing persons to risk. The problem posed by these imperatives is to decide when it is justifiable to seek certain benefits despite the risks involved, and when the benefits should be foregone because of the risks.

The obligations of beneficence affect both individual investigators and society at large because they extend both to particular research projects and to the entire enterprise of research. In the case of particular projects, investigators and members of their institutions are obliged to give forethought to the maximization of benefits and the reduction of risk that might occur from the research investigation. In the case of scientific research in general, members of the larger society are obliged to recognize the longer term benefits and risks that may result from the improvement of knowledge and from the development of novel medical, psychotherapeutic and social procedures.

The principle of beneficence often occupies a well-defined justifying role in many areas of research involving human subjects. An example is found in research involving children. Effective ways of treating childhood diseases and fostering healthy development are benefits that serve to justify research involving children—even when individual research subjects are not direct beneficiaries. Research also makes it possible to avoid the harm that may result from the application of previously accepted routine practices that on closer investigation turn out to be dangerous. But the role of the principle of beneficence is not always so unambiguous. A difficult ethical problem remains, for example, about research that presents more than minimal risk without immediate prospect of direct benefit to the children involved. Some have argued that such research is inadmissible, while others have pointed out that this limit would rule out much research promising great benefit to children in the future. Here again, as with all hard cases, the different claims covered by the principle of beneficence may come into conflict and force difficult choices.

3. Justice

Who ought to receive the benefits of research and bear its burdens? This is a question of justice in the sense of “fairness in distribution” or “what is deserved.” An injustice occurs when some benefit to which a person is entitled is denied without good reason or when some burden is imposed unduly. Another way of conceiving the principle of justice is that equals ought to be treated equally. However, this statement requires explication. Who is equal and who is unequal? What considerations justify departure from equal distribution? Almost all commentators allow that distinctions based on experience, age, deprivation, competence, merit and position do sometimes constitute criteria justifying differential treatment for certain purposes. It is necessary, then, to explain in what respects people should be treated equally. There are several widely accepted formulations of just ways to distribute burdens and benefits. Each formulation

mentions some relevant property on the basis of which burdens and benefits should be distributed. These formulations are: (1) to each person an equal share; (2) to each person according to individual need; (3) to each person according to individual effort; (4) to each person according to societal contribution; and (5) to each person according to merit.

Questions of justice have long been associated with social practices such as punishment, taxation and political representation. Until recently these questions have not generally been associated with scientific research. However, they are foreshadowed even in the earliest reflections on the ethics of research involving human subjects. For example, during the 19th and early 20th centuries, the burdens of serving as research subjects fell largely upon poor ward patients, while the benefits of improved medical care flowed primarily to private patients. Subsequently, the exploitation of unwilling prisoners as research subjects in Nazi concentration camps was condemned as a particularly flagrant injustice. In this country, in the 1940's, the Tuskegee syphilis study used disadvantaged, rural black men to study the untreated course of a disease that is by no means confined to that population. These subjects were deprived of demonstrably effective treatment in order not to interrupt the project, long after such treatment became generally available.

Against this historical background, it can be seen how conceptions of justice are relevant to research involving human subjects. For example, the selection of research subjects needs to be scrutinized in order to determine whether some classes (e.g., welfare patients, particular racial and ethnic minorities, or persons confined to institutions) are being systematically selected simply because of their easy availability, their compromised position or their manipulability, rather than for reasons directly related to the problem being studied. Finally, whenever research supported by public funds leads to the development of therapeutic devices and procedures, justice demands both that these not provide advantages only to those who can afford them and that such research should not unduly involve persons from groups unlikely to be among the beneficiaries of subsequent applications of the research.

C. Applications

Applications of the general principles to the conduct of research leads to consideration of the following requirements: informed consent, risk/benefit assessment and the selection of subjects of research.

1. *Informed Consent*

Respect for persons requires that subjects, to the degree that they are capable, be given the opportunity to choose what shall or shall not happen to

them. This opportunity is provided when adequate standards for informed consent are satisfied.

While the importance of informed consent is unquestioned, controversy prevails over the nature and possibility of an informed consent. Nonetheless, there is widespread agreement that the consent process can be analyzed as containing three elements: information, comprehension and voluntariness.

Information. Most codes of research establish specific items for disclosure intended to assure that subjects are given sufficient information. These items generally include: the research procedure, their purposes, risks and anticipated benefits, alternative procedures (where therapy is involved), and a statement offering the subject the opportunity to ask questions and to withdraw at any time from the research. Additional items have been proposed, including how subjects are selected, the person responsible for the research, etc.

However, a simple listing of items does not answer the question of what the standard should be for judging how much and what sort of information should be provided. One standard frequently invoked in medical practice, namely the information commonly provided by practitioners in the field or in the locale, is inadequate since research takes place precisely when a common understanding does not exist. Another standard, currently popular in malpractice law, requires the practitioner to reveal the information that reasonable persons would wish to know in order to make a decision regarding their care. This, too, seems insufficient since the research subject, being in essence a volunteer, may wish to know considerably more about risks gratuitously undertaken than do patients who deliver themselves into the hand of a clinician for needed care.

It may be that a standard of “the reasonable volunteer” should be proposed: the extent and nature of information should be such that persons, knowing that the procedure is neither necessary for their care nor perhaps fully understood, can decide whether they wish to participate in the furthering of knowledge. Even when some direct benefit to them is anticipated, the subjects should understand clearly the range of risk and the voluntary nature of participation.

A special problem of consent arises where informing subjects of some pertinent aspect of the research is likely to impair the validity of the research. In many cases it is sufficient to indicate to subjects that they are being invited to participate in research of which some features will not be revealed until the research is concluded. In all cases of research involving incomplete disclosure, such research is justified only if it is clear that: (1) incomplete disclosure is truly necessary to accomplish the goals of the research; (2) there are no undisclosed risks to subjects that are more than minimal and; (3) there is an adequate plan for debriefing subjects, when appropriate, and for dissemination of research results to them. Information about risks should never be withheld for the purpose of eliciting the cooperation of subjects, and truthful answers should always be given

to direct questions about the research. Care should be taken to distinguish cases in which disclosure would destroy or invalidate the research from cases in which disclosure would simply inconvenience the investigator.

Comprehension. The manner and context in which information is conveyed is as important as the information itself. For example, presenting information in a disorganized and rapid fashion, allowing too little time for consideration or curtailing opportunities for questioning, all may adversely affect a subject's ability to make an informed choice.

Because the subject's ability to understand is a function of intelligence, rationality, maturity and language, it is necessary to adapt the presentation of the information to the subject's capacities. Investigators are responsible for ascertaining that the subject has comprehended the information. While there is always an obligation to ascertain that the information about risk to subjects is complete and adequately comprehended, when the risks are more serious, that obligation increases. On occasion, it may be suitable to give some oral or written tests of comprehension. Special provision may need to be made when comprehension is severely limited—for example, by conditions of immaturity or mental disability. Each class of subjects that one might consider as incompetent (e.g., infants and young children, mentally disabled patients, the terminally ill and the comatose) should be considered on its own terms. Even for these persons, however, respect requires giving them the opportunity to choose to the extent they are able, whether or not to participate in research. The objections of these subjects to involvement should be honored, unless the research entails providing them a therapy unavailable elsewhere. Respect for persons also requires seeking the permission of other parties in order to protect the subjects from harm. Such persons are thus respected both by acknowledging their own wishes and by the use of third parties to protect them from harm.

The third parties chosen should be those who are most likely to understand the incompetent subject's situation and to act in that person's best interest. The person authorized to act on behalf of the subject should be given an opportunity to observe the research as it proceeds in order to be able to withdraw the subject from the research if such action appears in the subject's best interest.

Voluntariness. An agreement to participate in research constitutes a valid consent only if voluntarily given. This element of informed consent requires conditions free of coercion and undue influence. Coercion occurs when an overt threat of harm is intentionally presented by one person to another in order to obtain compliance. Undue influence, by contrast, occurs through an offer of an excessive, unwarranted, inappropriate or improper reward or other overture in order to obtain compliance. Also, inducements that would ordinarily be acceptable may become undue influences if the subject is especially vulnerable.

Unjustifiable pressures usually occur when persons in positions of authority or commanding influence—especially where possible sanctions are involved—urge a course of action for a subject. A continuum of such influencing factors exists, however, and it is impossible to state precisely where justifiable persuasion ends and undue influence begins. But undue influence would include actions such as manipulating a person's choice through the controlling influence of a close relative and threatening to withdraw health services to which an individual would otherwise be entitled.

2. Assessment of Risks and Benefits

The assessment of risks and benefits requires a careful array of relevant data, including, in some cases, alternative ways of obtaining the benefits sought in the research. Thus, the assessment presents both an opportunity and a responsibility to gather systematic and comprehensive information about proposed research. For the investigators, it is a means to examine whether the proposed research is properly designed. For a review committee, it is a method for determining whether the risks that will be presented to subjects are justified. For prospective subjects, the assessment will assist the determination whether or not to participate.

The Nature and Scope of Risks and Benefits. The requirement that research be justified on the basis of a favorable risk-benefit assessment bears a close relation to the principle of beneficence, just as the moral requirement that informed consent be obtained is derived primarily from the principle of respect for persons. The term “risk” refers to a possibility that harm may occur. However, when expressions such as “small risk” or “high risk” are used, they usually refer (often ambiguously) both to the chance (probability) of experiencing a harm and the severity (magnitude) of the envisioned harm. The term “benefit” is used in the research context to refer to something of positive value related to health or welfare. Unlike “risk,” “benefit” is not a term that expresses probabilities. Risk is properly contrasted to probability of benefits and benefits are properly contrasted with harms rather than risks of harm. Accordingly, so-called risk-benefit assessments are concerned with the probabilities and magnitudes of possible harms and anticipated benefits. Many kinds of possible harms and benefits need to be taken into account. There are, for example, risks of psychological harm, physical harm, legal harm, social harm and economic harm and the corresponding benefits. While the most likely types of harms to research subjects are those of psychological or physical pain or injury, other possible kinds should not be overlooked.

Risks and benefits of research may affect the individual subjects, the families of the individual subjects and society at large (or special groups of subjects in society). Previous codes and Federal regulations have required that risks to sub-

jects be outweighed by the sum of both the anticipated benefit to the subject, if any, and the anticipated benefit to society in the form of knowledge to be gained from the research. In balancing these different elements, the risks and benefits affecting the immediate research subject will normally carry special weight. On the other hand, interests other than those of the subject may on some occasions be sufficient by themselves to justify the risks involved in the research, so long as the subjects' rights have been protected. Beneficence thus requires that we protect against risk of harm to subjects and also that we be concerned about the loss of the substantial benefits that might be gained from research.

The Systematic Assessment of Risks and Benefits. It is commonly said that benefits and risks must be “balanced” and shown to be “in a favorable ratio.” The metaphorical character of these terms draws attention to the difficulty of making precise judgments. Only on rare occasions will quantitative techniques be available for the scrutiny of research protocols. However, the idea of systematic, non-arbitrary analysis of risks and benefits should be emulated insofar as possible. This ideal requires those making decisions about the justifiability of research to be thorough in the accumulation and assessment of information about all aspects of the research, and to consider alternatives systematically. This procedure renders the assessment of research more rigorous and precise, while making communication between review board members and investigators less subject to misinterpretation, misinformation and conflicting judgments. Thus, there should first be a determination of the validity of the presuppositions of the research; then the nature, probability and magnitude of risk should be distinguished with as much clarity as possible. The method of ascertaining risks should be explicit, especially where there is no alternative to the use of such vague categories as small or slight risk, it should also be determined whether an investigator's estimates of the probability of harm or benefits are reasonable, as judged by known facts or other available studies.

Finally, assessment of the justifiability of research should reflect at least the following considerations:

- (i) Brutal or inhumane treatment of human subjects is never morally justified.
- (ii) Risks should be reduced to those necessary to achieve the research objective. It should be determined whether it is in fact necessary to use human subjects at all. Risk can perhaps never be entirely eliminated, but it can often be reduced by careful attention to alternative procedures.
- (iii) When research involves significant risk of serious impairment, review committees should be extraordinarily insistent on the justification of the risk (looking usually to the likelihood of benefit to the subject—or, in some rare cases, to the manifest voluntariness of the participation).

- (iv) When vulnerable populations are involved in research, the appropriateness of involving them should itself be demonstrated. A number of variables go into such judgments, including the nature and degree of risk, the condition of the particular population involved, and the nature and level of the anticipated benefits.
- (v) Relevant risks and benefits must be thoroughly arrayed in documents and procedures used in the informed consent process.

3. Selection of Subjects

Just as the principle of respect for persons finds expression in the requirements for consent, and the principle of beneficence in risk-benefit assessment, the principle of justice gives rise to moral requirements that there be fair procedures and outcomes in the selection of research subjects. Justice is relevant to the selection of subjects of research at two levels: the social and the individual. Individual justice in the selection of subjects would require that researchers exhibit fairness: thus, they should not offer potentially beneficial research only to some patients who are in their favor or select only “undesirable” persons for risky research. Social justice requires that distinction be drawn between classes of subjects that ought, and ought not, to participate in any particular kind of research, based on the ability of members of that class to bear burdens and on the appropriateness of placing further burdens on already burdened persons. Thus, it can be considered a matter of social justice that there is an order of preference in the selection of classes of subjects (e.g., adults before children) and that some classes of potential subjects (e.g., the institutionalized mentally infirmed or prisoners) may be involved as research subjects, if at all, only on certain conditions.

Injustice may appear in the selection of subjects, even if individual subjects are selected fairly by investigators and treated fairly in the course of research. Thus injustice arises from social, racial, sexual and cultural biases institutionalized in society. Thus, even if individual researchers are treating their research subjects fairly, and even if IRBs are taking care to assure that subjects are selected fairly within a particular institution, unjust social patterns may nevertheless appear in the overall distribution of the burdens and benefits of research. Although individual institutions or investigators may not be able to resolve a problem that is pervasive in their social setting, they can consider distributive justice in selecting research subjects.

Some populations, especially institutionalized ones, are already burdened in many ways by their infirmities and environments. When research is proposed that involves risks and does not include a therapeutic component, other less burdened classes of persons should be called upon first to accept these risks of research, except where the research is directly related to the specific conditions

of the class involved. Also, even though public funds for research may often flow in the same directions as public funds for health care, it seems unfair that populations dependent on public health care constitute a pool or preferred research subjects if more advantaged populations are likely to be the recipients of the benefits.

One special instance or injustice results from the involvement of vulnerable subjects. Certain groups, such as racial minorities, the economically disadvantaged, the very sick and the institutionalized may continually be sought as research subjects, owing to their ready availability in settings where research is conducted. Given their dependent status and their frequently compromised capacity for free consent, they should be protected against the danger of being involved in research solely for administrative convenience, or because they are easy to manipulate as a result of their illness or socioeconomic condition.

GLOSSARY

Active Implantable. Any medical device that, in order to function, relies on a source of electrical energy or any other source of power other than that directly generated by the human body or gravity which is intended to be totally or partially introduced, surgically or medically, into the human body or by medical intervention into a natural orifice, and which is intended to remain after the procedure.

Administrative Proceeding. An action or proceeding that occurs in accordance with established procedures in order to issue, amend or revoke a regulation or order, or to take or refrain from taking any other form of administrative action against a product or person.

Advertising. The process by which information about a medical device is made generally or publicly known, usually to encourage people to buy or use it. Most if not all advertising, what may include promotional materials, is considered labeling. (See “Labeling”).

Audit. A systematic, independent examination of a manufacturer’s quality system that is performed at defined intervals and at sufficient frequency to determine: (1) whether both quality system activities and the results of such activities comply with quality system procedures; (2) that these procedures are implemented effectively; and (3) that these procedures are suitable to achieve quality system objectives.

Banning. An established procedure that a regulatory control authority may use to institute proceedings to ban a medical device intended for human use that presents substantial deception or an unreasonable and substantial risk of illness or injury which cannot be corrected or eliminated by labeling or change in labeling.

Biological(s). Any virus, therapeutic serum, toxic, antitoxin, vaccine, blood, blood component or derivative, allergenic product or analogous product, or arsphenamine or its derivatives (or any other trivalent organic arsenic compound), applicable to the prevention, treatment or cure of diseases or injuries in humans.

CE Mark. “Communaute Europeen” (CE) mark is required for all medical devices marketed in the European Union indicating that they meet common standards of performance and safety, known as essential requirements.

Civil Money Penalty. A monetary fine levied against a person found to be in violation of laws and/or companion regulations or other statutes enforced by a regulatory control authority.

Clinical Trial. A clinical investigation or research study involving one or more human subjects which generates clinical data to be used to demonstrate the safety and effectiveness of a medical device.

Commercialization (also Sale). Any distribution of a medical device intended for human use which is held or offered for sale.

Conflict-of-Interest (also Independence). Means to be impartial and free from any real or perceived commercial or financial interest or other pressures that might compromise the independence or objectivity of a regulatory control authority in making public health decisions or taking regulatory action.

Contract Sterilizer. A person who provides a sterilization service for medical devices manufactured by another person.

Corrective Action. Refers to the repair, modification or adjustment of a violative condition, or the repair, modification, adjustment, relabeling, removal or destruction of a violative product.

Criminal Prosecution. A legal action, typically resulting in imprisonment and/or monetary fines, that is directed against a person to punish past behavior, deter similar behavior in the future, and obtain future compliance.

Debarment (also Debar). An administrative sanction that a regulatory control authority can initiate against a person for inappropriate conduct relating to the development or approval of a medical device application. Debarment prohibits such persons from submitting or assisting in the submission of any market application for medical devices.

Design Control. An interrelated set of practices and procedures that are incorporated into the initial design and development process (i.e., a system of checks and balances). Design control assures a systematic assessment of the design an integral part of development of a finished medical device. As a result, deficiencies identified in design input requirements, in addition to discrepancies between proposed designs and requirements, are made evident and corrected earlier in the development process, increasing the likelihood that a design transferred to production will result in a medical device that is appropriate for its intended use.

Detention. An administrative action by which a regulatory control authority requires imported articles that appear violative under laws it administers to be held intact until such time as they are brought into compliance or determined to not be subject to applicable laws, or refused entry if they are not brought into compliance.

Distributor. Any person who furthers the marketing of a medical device from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer or user, but does not repackage or otherwise change the container, wrapper or labeling of the device, or the device package. This definition encompasses, but is not limited to, persons engaged in direct sales, mail orders, leasing, distribution of promotional samples, distribution of demonstration units, and drop shipping. The term “distributor” excludes brokers or other persons who merely perform a service for a person (other than the ultimate consumer) who owns a device.

Effectiveness (also Efficacy). Evidence that a medical device produces an intended clinical effect in a target population, usually from valid scientific research.

Emergency Order. A command or request by a regulatory control authority as a result of an unexpected occurrence or set of circumstances that threatens public health and demands immediate attention.

Establishment. A place of business under one management at one general physical location at which a medical device is manufactured, assembled, held, stored, packaged or otherwise processed.

Facility. Any factory, warehouse, store, pharmacy, hospital, carrier, vessel or any other location or establishment at which a medical device is manufactured, processed, imported, packed, refurbished, held, distributed, dispensed or sold.

FDA Approval. A generic term applied to an application for premarket approval (PMA) that has received consent from the United States Food and Drug Administration to place a medical device into commercial distribution.

Feasibility Study. An initial limited study conducted at the conceptual stage of a medical device to confirm its design and operating specifications before beginning an extensive clinical trial.

Global Harmonization Task Force. A multinational consortium formed in 1992 for the purpose of converging (i.e., harmonizing) national medical device regulatory requirements among members to improve public health protection practices, facilitate international trade, promote technological innovation and provide a model for nations with emerging device regulatory systems. The United States, European Union, Canada, Japan and Australia are “Founding Members” of the GHTF. (Additional information about the GHTF can be obtained from its Internet Web site: www.ghtf.org.)

Good Laboratory Practices (GLPs). Regulations that govern the practices used in non-clinical studies and are intended to ensure the quality and integrity of safety data used to support applications for medical device research or marketing applications.

Good Manufacturing Practices (GMPs). See Quality Systems.

Guideline. A non-binding document intended to assist persons with the interpretation of laws and/or regulations.

Implantable. A medical device that is placed into a surgically or naturally formed cavity of the human body and intended to remain there for a period of 30 days or longer. A regulatory control authority may, in order to protect the public health, determine that devices placed in humans for shorter periods of time are also “implantables.”

Importer. Any person who furthers the marketing of a medical device from a foreign manufacturer to the person who makes the final delivery or sale of the device to the ultimate consumer or user, but does not repackage or otherwise change the container, wrapper or labeling of the device, or the device package.

Invasive/Non-Invasive. Means a device or procedure that, by design or intention: (1) penetrates or pierces the skin or mucous membranes of the body, the ocular cavity or the urethra; or (2) enters the ear beyond the external auditory canal, the nose beyond the nares, the mouth beyond the pharynx, the anal canal beyond the rectum or the vagina beyond the cervical os.

In Vitro Diagnostic Device. Reagents, instruments and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat or prevent disease. Such products are intended for use in the collection, preparation and examination of specimens taken from the human body.

Investigational Device. A medical device that is the object of a clinical investigation to evaluate safety and effectiveness.

Labeling (also Label). Means all labels and other written, printed or graphic material that: (1) is affixed to a medical device or any of its containers or wrappers; or (2) accompanies a medical device. Labeling may include promotional material for a device.

Listing. A notification to a regulatory control authority from a manufacturer, importer, or specification developer indicating that it manufactures or has developed a type of medical device or imports a device into the country.

Manufacturer. Any person who designs, manufactures, fabricates, assembles or processes a finished medical device. The term “manufacturer” also refers to, but is not limited to, persons who perform the functions of contract sterilization, installation, relabeling, remanufacturing, repacking or specifications development, in addition to initial distributors of devices on behalf of foreign entities.

Market Entry Notification (also Premarket Notification). An application submitted to a regulatory control authority for the purpose of obtaining clearance to commercially market a new or modified medical device in that jurisdiction.

Medical Device (also General Medical Device). Refers to an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent or other similar or related article, including any component, part or accessory intended for human use, which is: (1) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment or prevention of disease; or (2) intended to affect the structure or any function of the body, and does not achieve its primary intended purpose(s) through chemical action within or on the body, and which is not dependent on being metabolized to achieve its primary intended purpose(s).

Packer. A person who packages ready-made products that meet the definition of a medical device and must handle such devices in conformance with good manufacturing practices.

Performance. When a medical device functions as intended in accordance with associated labeling and is in conformance with applicable technical specifications and relevant product standards.

Person. Any individual, partnership, corporation, association, scientific or academic establishment, government agency or organizational unit of a government agency, or any other legal entity.

Pharmaceuticals [also Drug(s)]. Means: (1) articles intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease in humans; (2) articles (other than food) intended to affect the structure or any function of the body; and (3) articles intended for use as a component of any articles specified in clauses (1) and (2) of this definition.

Physical Destruction. Procedures used to render medical devices unusable, such as burning, burial, crushing, grinding, etc.

Policy. A principle, plan or course of action pursued by a government, organization or individual.

Post-Market Surveillance. A term that some use synonymously with “post-market vigilance” (see below) while others use the term to refer to a process by which selected medical devices, whose long-term performance could not feasibly be demonstrated during the premarket testing stage, require closer scrutiny after marketing, usually by means of controlled post-market studies, patient registries or other measures.

Post-Market Vigilance. A process used to monitor the clinical performance of medical devices in actual use.

Premarket Evaluation. A process by which a regulatory control authority or surrogate accredited review entity reviews a market application leading to a judgment as to whether the safety and effectiveness of a new medical device has been adequately demonstrated.

Prescription Use. A medical device which, because of a potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, is not safe except when used under the supervision, or by order, of a practitioner licensed by law and for which adequate directions for safe use by consumers cannot be developed.

Processor. A person who processes ready-made products that meet the definition of a medical device and must manufacture medical devices in conformance with good manufacturing practices. (See “Manufacturer”).

Process Validation. A means to establish, by objective evidence, that a process consistently produces a result or a medical device that meets its pre-determined specifications.

Public Warning. A communication issued by a manufacturer, distributor, importer, regulatory control authority or other responsible party to alert users of a medical device about unforeseen and/or serious problems or risks associated with use of the device.

Quality Systems (also Good Manufacturing Practices). An umbrella term that refers to procedures that specify general objectives rather than methods associated with the manufacture, storage, holding, processing and handling of medical devices. These procedures address the organizational structure, responsibilities, processes and resources for implementing quality management requirements associated with medical device manufacturing.

Recall. The removal of a medical device from commercial distribution, or the field correction of a marketed device, including its labeling and promotional material, or the notification of risks to users of such a device which a regulatory control authority deems to be violative of the law(s) it administers and against which it would initiate legal action.

Records. Anything that is written down and preserved as evidence to verify regulatory compliance by a person and/or conformance of a medical device to national regulatory requirements. This includes electronic records.

Registration. A required filing with a regulatory control authority to identify the establishment seeking to market a medical device within the jurisdiction of the authority.

Refurbisher (also Remarketer). Any person who, for the purpose of resale or redistribution, visually inspects, functionally tests and services medical devices, as may be necessary, to demonstrate that a device is in good repair and performing all of the functions for which it

was designed. This may include cosmetic enhancement of the device and the performance of prevention maintenance. Refurbishers do not significantly change the performance, safety specifications or intended use(s) of a finished device.

Regulation. A rule, ordinance or requirement, established, controlled or directed, to assure consistent interpretation by persons relating to the manufacture, distribution, importation and processing of medical devices.

Regulatory Control Authority. An entity empowered to act on behalf of a national government (in most countries, these are departments within or affiliated with the ministry of health) to ensure that the requirements of medical device laws are properly carried out in that jurisdiction.

Relabeler. A person who changes the content of the labeling for a medical device from that supplied by the original manufacturer for distribution under the establishment's name. A relabeler does not include establishments that do not change original labeling but merely add their own name.

Restricted Use. A medical device for which a regulatory control authority has restricted the sale, distribution or use upon the written or oral authorization of a health practitioner licensed by law to administer or use the device, or upon such other conditions as the regulatory control authority may prescribe.

Reuse (also Reprocessing). Refers to use of a medical device more than once on the same or multiple patients. Action necessary for reuse of a device may include instructions for assembly/disassembly, on-site sterilization or disinfection, etc. This definition does not apply to the refurbishing or repair of a device for the purpose of redistribution or resale.

Safety. Means the benefits of a medical device to a patient undergoing medical diagnosis or treatment outweigh the risks of the product doing harm to the patient.

Seizure. An action by a regulatory control authority to take control of and, if necessary, remove a medical device from commerce because it is in violation of national laws and/or regulations.

Sponsor. A person who initiates, but does not conduct a clinical investigation: that is, an investigational device is administered, dispensed or used under the immediate direction of another person.

Tracking. A process to ensure that manufacturers of certain medical devices establish a system to enable them to promptly locate specific devices in commercial distribution. Tracking information can be used to facilitate notifications and recalls ordered by a regulatory control authority in cases when devices are determined to pose serious health risks.

Warning Letter. An official advisory issued to a person that communicates the position of a regulatory control authority on a matter which, if left uncorrected, could result in serious health consequences and appropriate enforcement action(s).

REFERENCES

- Annual Summary Report 1996 on Basic Medical Equipment Needs In the Newly Independent States, WHO European Information Service on Medical Supplies; September 15, 1996.
- “Assessing the Efficacy and Safety of Medical Technologies,” Office of Technology Assessment, United States Congress; OTA-H-75; September 1978.
- “Assignment of Agency Component for Review of Premarket Applications,” Federal Register, Vol. 56, No. 225, United States Department of Health and Human Services, Food and Drug Administration; November 21, 1991.
- “Basic Documents” - Fortieth Edition, World Health Organization; 1994.
- Brochure on “Ethics and Professionalism,” International Association of Medical Equipment Remarketers.
- “Clinical Trials: An Introduction,” Kshitij Mohan, Ph.D. and Harold E. Sargent, Medical Device and Diagnostic Industry; January 1996.
- Conference Proceedings - “International Conference on the Reuse of Disposable Medical Devices In the 1980’s”; March 1984.
- “Council Directive Concerning Medical Devices,” Commission of the European Communities; June 1993.
- “Council Directive On the Approximation of the Laws of the Member States Relating to Active Implantable Medical Devices” (as amended); Commission of the European Communities; January 1994.
- Draft Document: “European Union Study on EU Medical Devices Industry.”
- “Enforcement Priorities Guidance on Reuse of Single-Use Devices,” United States Food and Drug Administration; August 2000.
- “Federal Policies and the Medical Devices Industry,” Office of Technology Assessment, United States Congress; OTA-H-2291; October 1984.
- “Final Document On A Review of Selected Medical Device Applications,” Committee for Clinical Review, United States Food and Drug Administration; March 1993.
- Global Harmonization Task Force (Medical Devices), Lisbon, Portugal Meeting; October 8, 1996.
- Global Harmonization Task Force Documents:
- “Essential Principles of Safety and Performance of Medical Devices” [SG1-N020R4].
 - “Labelling for Medical Devices” [SG1-N009R6].
 - “Role of Standards In Assessment of Medical Devices” [SG1-N012R10].

- “Minimum Data Set for Manufacturer Reports to the National Competent Authority” [SG2-N7R1].
 - “Guidance on How to Handle Information Concerning Vigilance Reporting Related to Medical Devices” [SG2-N8R4].
 - “Global Medical Devices Vigilance Report” [SG2-N9R5].
 - “National Competent Authority Report Criteria” [SG2-N21R8].
 - “Manufacturer Trend Reporting on Post-Market Medical Device Associated Adverse Events” [SG2-N36R4].
 - “Adverse Event Reporting Guidance for the Medical Device Manufacturer Or Its Authorized Representative” [SG-2-N21R8].
 - “Guidance on Quality Systems for the Design and Manufacture of Medical Devices” [SG3-N99-8].
 - “Design Control Guidance for Medical Device Manufacturers” [SG3-N99-9].
 - “Process Validation Guidance for Medical Device Manufacturers” [SG3-N99-10].
 - “Guidelines for Regulatory Auditing of Quality Systems of Medical Device Manufacturers: Part 1-General Requirements” [SG4-99-28].
 - “Audit Language Requirements” [SG4-99-14].
 - “Training Requirements for Auditors” [SG4-00-3].
- “How FDA Is Causing A Technological Exodus - A Comparative Analysis of Medical Device Regulation: United States, Europe, Canada and Japan,” Robert Higgs, Ph.D., The Independent Institute; February 1995.
- “Managing the Medical Arms Race - Innovation and Public Policy In the Medical Device Industry,” Susan Bartlett Foote, J.D.; 1992.
- “Medical Device Industry Fact Book” - 3rd Edition; 1996.
- “Medical Device Regulation - Too Early to Assess European System’s Value as Model for FDA”; Document to the Chairman, Committee on Labor and Human Resources, United States Senate (GAO/HEHS-96-65); United States General Accounting Office; March 1996.
- “Medical Device Regulation In Australia”; 1995 and 1996 Presentations.
- “Medical Devices: A Legislative Plan”; Document of the Study Group on Medical Devices, United States Department of Health, Education and Welfare; September 1970. “Medical Devices: International Perspectives on Health and Safety,” C.W.D. Van Gruting, Pharm.D.; 1994.
- “Medical Devices In Europe - Reference Documents/Contact Points,” European Commission - Directorate-General III - Industry; July 1994.
- “Medical Device Regulation In the European Union,” Linda R. Horton, J.D.; United States Food and Drug Administration; September 1995.”

- “Medical Technology - Quality Assurance Needs Stronger Management Emphasis and Higher Priority,” Document to the Chairman, Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, United States House of Representatives; United States General Accounting Office; GAO/PEMB-92-10; February 1992.
- “Medical Technology - Quality Assurance Systems and Global Markets,” Document to the Chairman, Subcommittee on Health and the Environment, Committee on Energy and Commerce, United States House of Representatives; United States General Accounting Office; GAO/PEMB-93-15; August 1993.
- “Model Product Approval System for Rapidly Emerging Markets,” Health Industry Manufacturers Association; January 1996.
- “New Medical Devices: Invention, Development and Use,” National Academy of Engineering, Institute of Medicine; 1988.
- “Notified Bodies,” Commission of the European Communities; Revision 3; June 1992.
- “Proceedings of the First International Conference of Medical Device Regulatory Authorities,” World Health Organization, Pan American Health Organization, United States Food and Drug Administration; June 2-6, 1986.
- “Proposed Regulatory Requirements for Medical Devices Sold In Canada,” Document of Working Group #4, Medical Devices Bureau, Environmental Health Directorate, Health Protection Branch; January 1995.
- “Protecting Human Research Subjects: Human Subjects Research Handbook,” United States Department of Energy, Office of Health and Environmental Research; January 1996.
- “Regulating Change: The Regulation of Foods, Drugs, Medical Devices and Cosmetics In the 1990’s; Jonathan C. Peck, J.D., and Kenneth C. Rabin; 1989.
- “Regulatory Cooperation: The U.S. Food and Drug Administration’s Agreements With Other Countries’ Counterparts,” Linda R. Horton, J.D.; 1996.
- Sixth Global Medical Devices Conference: Access To Global Markets Through Balanced Regulation; October 9-10, 1996.
- “The Case Against Reuse of Single Use Medical Devices,” European Confederation of Medical Devices Associations (EUCOMED).
- “The Medical Device Industry - Science, Technology and Regulation In A Competitive Environment,” Norman F. Estrin, Ph.D.; 1990.
- “The Principles of Good Clinical Study Design,” Richard P. Chiacchierini, Ph.D.; January 1994.
- “The Reuse of Hemodialyzers: An Assessment of Safety and Potential Savings,” Enis Banis, M.D., MSc., and Maurice McGregor, M.D.; Conseil _evaluation des technologies de la sant_ de Quebec.

“The Use of Essential Drugs” - Sixth Document of the WHO Expert Committee, World Health Organization; 1995.

“WHO Pharmaceuticals Newsletter,” No. 11/12 - November/December 1995 and No. 7; July 1995.