INSTITUTE OF PHYSICS

MEDICAL DEVICE SAFETY

The Regulation of Medical Devices for Public Health and Safety

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IoP

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Preface

Medical devices developed during the past thirty years—such as pacemakers, hip implants, medical resonance imagers—have transformed the lives of millions of patients, often restoring their life expectancy and quality of life to that of normal healthy people.

At the same time, well-publicized problems with heart valves, breast implants and other products have given rise to unease about the safety of medical devices. The public rightly expects safety to be the first priority of both manufacturers and health authorities but has little or no appreciation that absolute safety cannot be guaranteed.

In this book I have described the approaches taken in several countries to assure the safety of medical devices. These have developed rapidly in attempts to keep pace with the astonishing rate of introduction of new devices. Although the regulations in force throughout the world appear quite different, this appearance is superficial and the fundamental approaches are very similar. I have attempted to emphasize the common and key elements to be found in the various regulatory systems and to build on them to describe a possible 'global' system.

The regulation of medical devices is both a technical and legal matter. Technical rules for safety have to be agreed by experts and to be changed as the technology develops; these rules have to be enforced by legal means. The development of international technical rules by the international standards bodies has reduced confusion and argument and is scientifically and economically beneficial.

The kind of cooperation that has been successful on the technical level is needed also in the legal field if unnecessary duplication and controversy are to be removed. Considerable success in harmonizing regulations has been achieved in Europe and South America and the harmonization process is now being actively pursued on an international level in the Global Harmonization Task Force which includes both regulatory authorities and manufacturers.

After spending some thirty years promoting international harmonization by participation in international standards committees, it is being involved in the initiation of the GHTF which gives me greatest satisfaction. The degree of commitment shown by the members has been remarkable and has led to the appearance, in an astonishingly short time, of a framework for an economical and effective world-wide system of regulation for medical devices. I am optimistic that the next decade will see such a system brought into widespread use.

Gordon R Higson
Banchory, UK
February 2001

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This book is largely based on a thesis submitted for the degree of PhD at the University of Aberdeen in 2000. I wish to record my thanks to my supervisors, Professor P F Sharp and Dr A I L Campbell, for their advice and encouragement; to Quintiles–MTC for access to documents; to colleagues in Quintiles–MTC (particularly Caroline Freeman) and FDLI for the provision of documents and other information; and to my wife, Eileen, for her forbearance during the past four years.

In memoriam

Gordon Higson died suddenly on 9 August 2001 following a second stroke soon after approving the final proofs of this book.

He was born in Bolton, Lancashire in 1932 and gained a physics degree from Manchester University. After working in the aircraft and coal mining industries, he joined the Scientific and Technical Branch of the UK Department of Health and Social Security in 1969. He became Director of the Branch in 1980 and was responsible for the development of the UK approach to the regulation of medical devices.

On leaving the DHSS in 1988 he became Secretary General of the International Association of Medical Prosthesis Manufacturers (IAPM)—an association of the manufacturers of critical implantable medical devices with a particular interest in promoting an appropriate legal and regulatory environment for such devices. Here he spearheaded the IAPM's input to the development of the European Medical Devices Directives.

In 1989 he co-founded Medical Technology Consultants Europe Ltd (now part of Quintiles TransNational Corporation) and was Chairman of the company until 1995. He was a Non-executive Director of Vickers Medical from 1989 to 1993.

Gordon was a passionate advocate of national and international standards for many years. He was chairman of the BSI Healthcare Standards Committee 1983–91, Chairman of IEC Sub-Committee 62C 1982–92 and Chairman of ISO Technical Committee 210 1994–98. He was a founder of the Global Harmonization Task Force and consultant to the European Commission on Harmonization Issues 1992–96. He was also the author of *The Medical Devices Directives—a Manufacturer's Handbook* (MTC, 1st edition 1994, 2nd edition 1996) and of more than 100 papers and he made presentations at conferences world wide.

Gordon was also a family man, a constant source of support to his wife, three children and seven grandchildren. He was known for his energy,

determination, humour and generosity, a man of great humanity who will be missed by family, friends and colleagues alike.

Mark Higson
Farnham Common, UK
September 2001

Foreword

In the past three decades there has been an explosion in the use of medical technologies to enhance diagnosis and improve therapy for the benefit of the patient. Associated with this expansion of the many applications of devices has been the increased attention paid by government regulatory bodies around the world to the safety and effectiveness of these products. The United States started this regulatory oversight with the 1976 Medical Device Amendments to the Federal Food, Drug and Cosmetic Act, and soon other governments, including the European Community, were developing similar programs. The various regulators' schemes have consistently been amended to accommodate the changing perspectives of safety. In addition to the formal published regulations, the various governments have made use of other guidelines and pronouncements that amplify the original regulations. Collectively these requirements may appear as a formidable hurdle for conscientious manufacturers to commercialize their products around the world.

There are numerous books and articles devoted to helping the medical device industry understand the complexities and requirements of the various regulatory bodies. The need to navigate through these international regulatory shoals is extremely important to any medical device company—but especially important to a small start up company that is attempting to 'go global'. Gordon Higson has prepared a text that clearly outlines the current regulatory situation in the European Community, the United States, Japan and other countries, and is a guide for any manufacturer planning to export into the world market.

The book describes the evolution of regulations from early treatment of devices such as pharmaceuticals to an 'engineering approach' and the use of 'key' features to assure the safety and effectiveness of the products. Higson points out that the future global system should be an evolution that incorporates the requirements of a risk-based classification scheme, application (dossier) preparation, submission, and testing and post market controls.

Quality systems, product standards, and effectiveness are discussed in separate chapters to emphasize the alternatives used in different countries. International cooperation among regulatory agencies culminated (1992) in the Global Harmonization Task Force that should set the way for the future with a universal medical device regulatory system. However, in the meantime, it is important that corporations entering into the world market understand and utilize the information that is contained in this valuable reference.

John C Villforth
President, Food and Drug Institute and former
Director, FDA's Center for Devices and Radiological Health

Chapter 1

Introduction

Medical products of all kinds have to comply with regulations to satisfy the demand for public health and safety. Medicinal products (drugs) were the first medical products to be regulated in most countries and regulations for medical devices followed—initially generally derived from drug regulations.

This book describes and examines legislation regulating the sale and use of safe medical devices. It concentrates on the situation in the European Community,[1] Japan and the USA as these three countries/regions together constitute some 85% of the world market for medical devices (HIMA 1997).[2] The regulatory situation in several other countries is briefly described. It deals with the relatively new EC Directives on medical devices in some detail because the history of their creation demonstrates that a harmonization process that many people thought would be impossible can occur successfully, and because these Directives provide the basis of a model for a future world-wide regulatory system.

Four key features of, and areas of controversy in, recent legislation are discussed at some length in Chapters 6 to 9 and their importance in the regulatory scheme is assessed. This leads to a set of proposals for a rational regulatory system which could be applied world-wide, thus simplifying the demands on manufacturers, easing technical barriers to trade, reducing the cost of meeting regulatory requirements and, by concentrating global expertise, actually increasing the level of public health and safety in so far as they are influenced by medical devices.

[1] The terms European Union and European Community are generally used interchangeably but, as the medical devices Directives were introduced under the EC Treaty, the terms EC and European Community will be used throughout.

[2] References are identified by a name, or initials, and a date. They will be found at the end of the thesis, listed in alphabetical and date order.

History

The history of medical device regulation is a short one and essentially begins with the passing in the United States of the Medical Device Amendments (to the Federal Food, Drug and Cosmetic Act) in 1976 (USA 76a). Before the Second World War, legislation existed in very few countries (Italy 27, USA 38), and such legislation was so general as to have little effect. In fact there was no demand for medical devices to be regulated as, until the 1950s, few medical devices existed which offered any appreciable risk to patients or users. A notable exception was X-ray equipment. The risks presented by ionizing radiation had been appreciated for some years and regulations, based on the recommendations of the International Commission on Radiological Protection (ICRP 51), governing the exposure of workers to ionizing radiation and enforcing the shielding of radiation sources, were introduced in several countries.

The next risk to be recognized was that of infection from improperly sterilized devices used for the injection or infusion of medicines or which otherwise penetrated the natural bodily defences. Legislation controlling the sale of sterilized medical devices was introduced from the 1960s, commonly under pre-existing legislation for the safety of drugs.

The only other types of medical devices receiving appreciable regulatory attention until recently were those powered by electricity, but the coverage and nature of the regulations varied from country to country.

The first really comprehensive medical device legislation in a modern form was the US Medical Device Amendments of 1976. They have had a profound influence on the design and manufacture of medical devices but, although they were updated by several revising Acts and regulations, remain somewhat limited in some ways and have been criticized by George (1994) among others. These criticisms have been addressed to some extent by the FDA Modernization Act of 1997 (USA 97a) (see Chapter 4).

The other major development in medical device regulation was the introduction of the European medical device Directives in the years 1993–98. These Directives constitute the most recent major medical device legislation in the world. The most important (in terms of its coverage) of these is the EC Directive on Medical Devices, 93/42/EEC (EC 93a), which is examined in detail in Chapter 3.

This Directive broke new ground in expanding the basic requirement that 'medical devices may be placed on the market and put into service only if they do not compromise the safety and health of patients, users and, where applicable, other persons . . .' into specific statements of what constitutes 'safety' in a list of 'Essential Requirements' appended to the Directive. It goes on to state that compliance with certain designated ('harmonized') standards is deemed to satisfy the legislative requirements. These are features of the 'New Approach' to product regulation in Europe

(EC 85b) and represent an engineering approach to the regulation of medical devices.

These novel features are now appearing in revised legislation being enacted in Canada, proposed in Australia, and under consideration in other countries. However, they bring the European regulations into sharp contrast with regulations, based on pharmaceutical controls, in some other countries.

The country of greatest interest is the United States which is the world's largest producer and consumer of medical devices (Wilkerson 1995) and which consequently has a major influence world-wide. The FDA Modernization Act of 1997 introduced some features which moved the US slightly towards the European approach but the major limitations still remaining are the lack of transparency in the US approval process, i.e. the criteria on which the judgements of safety and efficacy are made are not explicitly stated, and the extent to which studies of clinical effectiveness are pursued. These issues are discussed more fully later in this book.

Special features of medical products

Medical device legislation must be seen in the context of laws aimed at the protection of purchasers and users of goods of all kinds. These include laws protecting consumers against false or misleading descriptions, or imposing basic safety requirements on sellers or manufacturers of goods, such as general product safety and product liability.

General laws of this kind are supplemented by specific laws and regulations addressing certain categories of goods which are considered to present specific risks to their users, third parties or the environment. Products intended for medical purposes are specifically regulated in most, if not all, developed countries and many developing countries are currently introducing such legislation.

Medical products (both drugs and devices) are generally considered to require special measures because they are used on patients who have a lowered state of health, because they often penetrate the body's own protective barriers such as the skin, and because of their intimate connection—often over long periods—with sensitive organs and/or body fluids. Furthermore, because of their direct connection with the health of the patient, sometimes with a life-saving or life-sustaining function, it is not sufficient for a medical product simply not to cause harm (which is the case for most other products) but it must act in the way that the doctor or nurse prescribing or using it expects.

These considerations have generally led legislators to require that medical products be assessed in some way and identified as being safe and fit for use before being allowed on to the market.

Drugs versus devices

Protective legislation addressing medical products generally divides them into two distinct categories: drugs (medicinal products) and devices.

This separation is based on the different modes of action of drugs and devices which leads to quite different approaches to the establishment of their safety.

In general, drugs (medicinal products) are introduced directly into the bloodstream, the digestive system or the musculature and are conveyed to the internal organs of the body. The effects they will have on the organs, especially in repeated doses, can be predicted only roughly and may be dependent on the physical characteristics of the patient. Their true effects can only be discovered by tests on living systems: cells, animals, and ultimately human beings. These tests are aimed at establishing dose levels which are safe and effective for different types of patient, the possible presence of undesirable side effects and any contra-indications, i.e. conditions in which the drug should not be used. Side effects and contra-indications may become apparent long after the administration of the drug, and damage to organs may be irreversible. This means that patient observation must be continued for an appropriate period, also that the tests must involve appropriate numbers and types of patients in order that the information emerging from the tests should be well founded and capable of extrapolation to future patients.

By contrast, medical devices generally have only physical effects on the body; these effects are usually independent of the patient's characteristics and they stop when the use of the device is discontinued. The effects of physical actions on the body are mostly known and safe (or, at least, acceptable) levels of actions such as radiation, electric current and temperature can be checked by laboratory examination. For devices which are in intimate contact with the body, such as implants, the absence of biological effects must be proven. This will certainly involve tests on living systems but test methods are available which make it possible to avoid tests on humans in many cases.

The repeatability of the characteristics of devices and the ability to transfer them from one device to another makes it possible to codify the safety requirements for many types of device in ways which can be universally applied. These codifications are generally formulated as standards.

Standards produced by international agreement are becoming increasingly important in medical device regulation, as discussed in Chapter 7, and offer the major hope for rationalizing national and regional regulatory approaches into a world-wide system (see Chapters 7 and 10).

The existence of such standards, which allow the safety of most medical devices to be relatively easily determined in an objective manner, is a major difference between devices and drugs and marks out medical devices as engineering products.

Of course, for devices which are life-saving or life-maintaining, or which introduce new technological features, tests on humans ('clinical investigations') must be carried out. These are generally on a much smaller scale than clinical investigations on drugs and may be carried out as much to establish the function of the device as its safety.

The extent to which the regulation of medical devices should extend beyond safety—to include requirements for performance, efficacy or effectiveness—remains controversial and is one of the issues examined later in this book.

Quality systems

Any judgement of the safety and satisfaction of a medical device can only be based on the examination of an example of the device itself or of an accurate technical description of the device. For that judgement to apply to all future manufacture of that device demands that every single device must be exactly the same as the examined example or technical description.

The requirement that medical device manufacturers should implement quality systems to ensure that this is the case was pioneered by the USA in its Medical Device Amendments of 1976 and its subsequent Good Manufacturing Practice Regulation (USA 78). It was followed by the United Kingdom with its voluntary Manufacturers' Registration Scheme (Higson 1994).

The use of good manufacturing practice, or quality systems, for manufacturing has become widespread but nowadays increasing emphasis is being given to quality systems for design and manufacture based on the international standard ISO 9001 (ISO 94a) as a component of a pre-market approval system (Higson 1995). The use of quality systems in this way offers important advantages to both manufacturers and regulators and makes them one of the 'key factors' I have identified in Chapters 6, 7, 8 and 9.

Product liability

The developing regulation of medical devices has been supported by corresponding developments in product liability legislation.

In Europe the Product Liability Directive 85/374EEC (EC 85a) introduced strict liability on producers of all kinds if damage or injury is caused by a defective product. A defective product is one which 'does not provide the safety which a person is entitled to expect, taking into account all of the circumstances'. This Directive has been implemented in all Member States of the European Community. Compliance with medical device regulations may be used in defence by manufacturers.

The situation is similar in the United States, where strict liability is recognized in most States. Any violation of FDA requirements may be used as evidence against the manufacturer in US product liability litigation.

For further details of product liability law in Europe, see Hodges (1993), and for product liability in the United States, see Gleason and Speights (1994).

Globalization

The differences in the approval mechanisms from country to country are a source of inefficiency and cost. Manufacturers have long complained about the waste of effort and the delays occasioned by having to make varied submissions for approval as they enter new markets—often accompanied by repeat testing which, in the worst case, may involve different national standards or even the need to make changes in an established device.

As the industry has become more globalized in its marketing, and as more countries have introduced medical device regulations, these problems have increased and demands for a more uniform world-wide regulatory system have intensified. Despite the scepticism often expressed about the possibility of achieving a global regulatory system for medical devices, much progress towards this goal has been made in the past ten years.

The first step in this direction was made in Europe where widely disparate national regulations were scrapped and replaced by completely new regulations which apply throughout the European Community and which provide that an approval process carried out once, in any part of the EC, applies throughout the Community. This was not an easy process and took some years but, as it shows that differences can be overcome, this process is described in some detail in Chapter 2.

Another regional system has been introduced in the countries of South America as a component of the MERCOSUR trading zone and an attempt is being made to prevent the spread of disparate regulations in the Far East by the 'Asia–Pacific Harmonization Group'. However, the most significant development has been the formation of the Global Harmonization Task Force in 1992. This group has been remarkably successful so far and offers the possibility of a largely unified regulatory system within the next ten years or so. The author is optimistic about the future of this group which is discussed in detail in Chapters 10 and 11.

Definitions

The discussions in this book will be based on definitions given in the European Community Directives 65/65/EEC (medicinal products) (EC 65),

93/42/EEC (medical devices) (EC 93a) and 98/79/EC (in vitro diagnostic products) (EC 98a).

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

Medical device: Any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application intended by the manufacturer to be used on human beings for the purpose of:

- the monitoring, treatment or alleviation of disease,
- the diagnosis, monitoring, treatment, alleviation or compensation for an injury or handicap,
- the investigation, replacement or modification of the anatomy or of a physiological process,
- the control of conception,

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means but which may be assisted in its function by such means.

The definition of a medical device given in EC Directive 93/42/EEC is the latest one to be found in a major piece of legislation. It drew on the definitions already existing in the Member States of the European Community and on those in other countries, particularly the USA. It is similar to other definitions of a medical device in making the prime characteristic the absence of pharmacologically-related action. A significant difference, which recognizes the growing use of drug-device combinations, is the reference to the *principal intended* action (which acknowledges that a device may be *assisted* in its function by pharmacological means).

This feature of the European definition of a medical device removes some of the difficulties of discriminating between a drug and a device, and helps with the regulation of drug–device combinations. Nevertheless, difficult cases remain and pose some of the most interesting problems in medical device legislation. Some of these issues are explored in the context of the drafting and operation of the EC Directives on medical devices in Chapters 2 and 3.

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