Quality System Requirements for Medical Devices

Reference Guide
for
Manufacturers Selling Medical Devices in Europe, Canada and the United States

2005 Version

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Aussi disponible en français sous le titre *Exigences en matière de système qualité pour les dispositifs médicaux: Manuel de référence à l'intention des fabricants qui vendent des dispositifs médicaux en Europe, au Canada et aux États-Unis - Version 2005*. Une version électronique du document français est disponible à l'adresse suivante : http://strategis.gc.ca/appmed .

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Introduction

In September 1997, Industry Canada's Health Industries Branch contracted with *Orion Canada Inc*. to develop a reference guide for Canadian companies presently selling or planning to sell medical devices in the European Union, Canada, or the United States. The original reference guide was published by Industry Canada's Health Industries Branch on April 27, 1998; a revised version was published on March 31, 2001 as significant changes had occurred in many areas. This change continues, resulting in this 2005 guide that has been updated as the industry globally moves ever closer towards harmonization for quality systems of medical devices.

The guide has proved to be extremely popular and Industry Canada contracted *Orion Canada Inc*. to update the guide once again. This 2005 version addresses current requirements; it is recommended to both those new to medical devices and experienced practitioners.

The rise of *ISO 13485: 2003 Medical devices - Quality management systems - Requirements for regulatory purposes* as the world standard, is important to understand. The standard was recently complemented, in late 2004, by the publishing of *PD ISO/TR 14969: 2004 Medical devices - Quality management systems - Guidance on the application of ISO 13485: 2003*.

The reference guide is not intended to be a "how to implement" guide for a particular standard. Rather, it should be viewed as a road map to help Canadian companies determine the quality standards that apply to their products.

This reference guide identifies and explains the quality requirements for the European Union, Canada and the United States as expressed in the following:

- Europe's *Council Directives 93/42/EEC* of 14 June 1993, concerning medical devices; and *98/79/EC* of 27 October 1998, concerning in vitro diagnostic medical devices; and *Commission Directives 2000/70/EC* of 16 November 2000, concerning Human Blood or Plasma; and *2003/32/EC* of 23 April 2003 with respect to medical devices utilizing tissues of animal origin.
- The *Canadian Medical Devices Regulations* (CMDRs)
- The United States' *FDA Quality System Regulation* (QSR)

This reference guide briefly describes other features of these jurisdictions, e.g., device classification, registering a quality system, selecting a registrar or notified body, post-market surveillance and problem reporting, labeling, EU representation, and the FDA's pre-market notification and pre-market approval. Useful information sources pertaining to each jurisdiction are also identified in the reference guide.

Chapter 1: The European Union Requirements

An Overview of the Quality Requirements for the Sale of Medical Devices in Europe

In 1985, Europe adopted a *New Approach to Technical Harmonization and Standards* to promote the free movement of goods among member states within the European Union. This replaced the existing product regulatory and safety requirements of individual member states with "essential requirements" covering all of Europe: European Community Directives (called *New Approach Directives*). The overview of the Directives was updated in the so-called "New Approach and Global Approach"; the list of relevant directives can be found at http://europa.eu.int/comm/enterprise/newapproach/legislation/directives1.htm

The Guide to the Implementation of Directives Based on New Approach and Global Approach at http://europa.eu.int/comm/enterprise/newapproach/legislation/guide/legislation.htm

Medical device specific summary at http://europa.eu.int/comm/enterprise/medical_devices/guide/index.htm

A brief summary on medical devices "New Approach" Directives, from an authoritative group, the Medical Devices Expert Group (MDEG) that is a part of medical device regulatory development in Europe, can be found at http://europa.eu.int/comm/enterprise/medical_devices/legal.pdf.

New Approach Directives with CE marking requirements have been written for more than 20 product groups, including medical devices, which are covered under the Medical Devices Directive 93/42/EEC, June 14, 1993 (MDD). This directive contains essential requirements concerning safety, health, environment and consumer protection; it became mandatory on June 14, 1998. European Community Directive 90/385/EEC, covering Active Implantable Medical Devices (AIMD), was first published on June 20 1990 and became mandatory on December 31 1994. The AIMD contains essential requirements (ERs) pertaining to active implantable medical devices.

More recently, directives for *in vitro* diagnostic medical devices, human blood and derivative products, a reclassification of breast implants and devices manufactured utilizing tissues of animal origin have been published:

- Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on *in vitro* diagnostic medical devices (here referred to as the IVD MDD, often referred to as the IVD Directive or IVDD by others);

- Directive 2000/70/EC of the European Parliament and of the Council of 16 November 2000 amending Council Directive 93/42/EEC as regards medical

devices incorporating stable derivatives of human blood or human plasma (here referred to as the Human Blood Directive);

- Commission Directive 2003/12/EC of 3 February 2003 on the reclassification of breast implants in the framework of Directive 93/42/EEC concerning medical devices (here referred to as the Breast Implant Reclassification Directive);

- Commission Directive 2003/32/EC of 23 April 2003 introducing detailed specifications as regards the requirements laid down in Council Directive 93/42/EEC with respect to medical devices manufactured utilizing tissues of animal origin (here referred to as the Animal Tissues Directive).

These directives and others can be located via the European Commission Europa web site at http://europa.eu.int/comm/enterprise/medical_devices/. This page has links with other useful documents referred to here or generally useful to all medical device manufacturers and it is a recommended bookmark.

These newer directives modify the MDD, and all should be read together for a complete understanding of all the changes. It is important to note the MDD is currently being amended as part of a five-year review process and so further changes are likely in the near future.

The **Medicines and Healthcare products Regulatory Agency** (**MHRA),** www.mhra.gov.uk/ that links into the devices section www.medical-devices.gov.uk/ , is the UK Competent Authority and all medical device work in regard to placing devices on the UK market is regulated by them. It is important to examine the available information at this site, especially in regard to guidance documents, bulletins and clinical trials. It is in English and the guidance documents are useful to read and understand for all European markets. Please see Appendix 5: List of Important Documents and Standards.

The primary focus of this chapter is on the MDD and IVD MDD as this covers the vast majority of medical devices, and the approach used under the MDD for Class III devices matches the expectations that European regulators have for active implantable medical devices. Specifics related to active implantable medical devices can be referred to in the AIMD and relevant harmonized standards.

Quality System Overview

As stated in the introduction **ISO 13485: 2003 Medical devices - Quality management systems - Requirements for regulatory purposes** has become the world standard for medical device quality systems and has now been recently complemented in late 2004 by the publishing of **PD ISO/TR 14969: 2004 Medical devices - Quality management systems - Guidance on the application of ISO 13485: 2003**.

The previous version of this guide referred to a number of changes that have occurred. Further changes have since occurred, making for an apparently complex situation that is in reality not so complex. To simplify the situation, this version concentrates on the current situation and does not discuss the historical background in detail; however, a statement about the key changes is clearly necessary.

- **EN ISO 13485: 2003 replaced the two earlier standards, EN ISO 13485: 2000 and EN ISO 13488: 2000.**

- **The earlier standards EN ISO 13485: 2000 and EN ISO 13488: 2000 will cease to provide presumption of conformity with relevant Essential Requirements on 31 July 2006 at the end of the agreed transition period.**

It is important to note **ISO 13485: 1996** Quality Systems – Medical devices – Particular requirements for the application of ISO 9001 **is no longer in use in Europe** and indeed cannot be purchased from the major standards bodies. However, the majority of requirements in the 2003 version are in practice very similar, although the changes have moved the standard to be in close compliance with US FDA QSR requirements provided the system is rigorously implemented.

- **ISO 13485: 2003 became a harmonized standard for all the medical device directives on the April 2, 2004.**

- **PD ISO/TR 14969: 2004 Medical devices - Quality management systems - Guidance on the application of ISO 13485: 2003 will soon become a harmonized standard for all the medical directives.**

There is no direct equivalent to EN ISO 13488: 2001 (that replaced EN 46002), as with ISO 9001: 2000 the manufacturer has to actively justify opting out of design controls that is now termed “product realization”. EN ISO 13485: 2003 does have two very helpful annexes that are considered particularly useful for Canadian based companies to refer to

- **Annex A (informative): Correspondence between ISO 13485: 2003 and ISO 13485: 1996;** and
- **Annex B (informative): Explanation of differences between ISO 13485 and ISO 9001: 2000.**

These informative annexes are further assisted by the annexes in ISO 14969: 2004 and all manufacturers are strongly recommended to study these and discuss them with their Notified Body:

- **Annex A (informative) Terms used in certain regulatory administration to describe documents referenced in this Technical Report;** and
- **Annex B (informative) Analysis of significant changes from ISO 13485: 1996 to ISO 13485: 2003;** [this has an extra column with explanations].

It is not mandatory to use EN ISO 13485: 2003 as the quality system standard, but any required system has to be equivalent to this or better; even the low risk Class I devices benefit from a quality system that is in effect the core management system for a medical device company. Notified Bodies prefer a well understood consistent system when auditing; as EN ISO 13485: 2003 is both the European harmonized standard and the emerging global standard, developed with the full assistance of the Global Harmonization Task Force (GHTF, www.ghtf.org) that includes the USA and Canada, it makes sense to use it.

This Reference Guide recommends the use of ISO 13485: 2003.

Global Harmonization Task Force

All readers are strongly encouraged to make full use of the free downloads of various related documents produced by the highly experienced group of experts that make up the GHTF. There are five main study groups in the GHTF:

Study Group 1:	*Regulatory Requirements, Labeling and Pre-market Review;*
Study Group 2:	*Adverse Event Reporting, Medical Device Vigilance and Post-Market Surveillance;*
Study Group 3:	*Quality Systems Requirements & Guidance;*
Study Group 4:	*Auditing;*
Study Group 5:	*Safety, performance, definitions and terminology used in clinical studies and related documentation.*

GHTF promotes convergence of regulatory requirements and this does include pre-market submissions including the pilot program identified as the STED initiative. It originates from a Global Harmonization Task Force (GHTF) document entitled: “Summary Technical Documentation for Demonstrating Conformity to the Essential Principles of Safety and Performance of Medical Devices (STED document)”. This document was developed by Study Group 1 and can be found under Proposed Documents: SG1-N011R17.

Directives: Mandatory CE Marking, Transitional Periods and Annexes

Compliance with essential requirements of the appropriate Directive(s) is mandatory before the CE marking can be legally placed on a product or associated labeling. Medical products not bearing the CE marking cannot be sold within the EU after the end of any transitional period that applies to the Directive concerned. **The transitional phase of the AIMD, MDD and IVD MDD has passed.**

For IVDs, the **IVD MDD** was published on December 7, 1998; became effective on June 7, 2000 and became mandatory, i.e., the transitional period ended on December 7, 2003. For a further two years, it is possible for IVDs that were placed on the market before December 7, 2003 without a CE marking to be put into service. After December 7, 2005, only CE marked IVD devices can be put into service, and interested persons are asked to note this is **not** an extension to the transitional phase but a mechanism to allow a product to legally work its way through the distribution chain.

Article 1 Scope, definitions of the IVD MDD states:

> "(i) 'placing on the market' means the first making available in return for payment or free of charge of a device other than device intended for performance evaluation with a view to distribution and/or use on the Community market, regardless of whether it is new or fully refurbished;
>
> (j) 'putting into service' means the stage at which a device has been made available to the final user as being ready for use on the Community market for the first time for its intended purpose."

The **Human Blood Directive** (Directive 2000/70/EC) is effectively an amendment of both the MDD and IVD MDD in regard to medical devices incorporating stable derivatives of human blood or human plasma. Note that a human blood derivative, "if used separately, may be considered to be a medicinal product constituent within the meaning of Council Directive 89/381/EEC," i.e., as a controlled pharmaceutical entity. Where a medical device or IVD is used in combination with a 'human blood derivative' the device or IVD must meet the relevant essential requirements of the relevant directive, even when regulated as a medicine. Note "Where a device incorporates, as an integral part, a human blood derivative, the notified body shall seek a scientific opinion from the European Agency for the Evaluation of Medicinal Products (EMEA) on the quality and safety of the derivative, taking account of the intended purpose of the device." Batch release certificates from a State or designated laboratory are a requirement of this directive.

Member States mostly published their laws to implement the Human Blood Directive by December 13, 2001 and applied it from June 13, 2002. The transitional period is for five years, i.e., until June 13, 2007; with a further two years until June 13, 2009 for devices to be put into service (as similarly done for the IVD MDD). No more discussion is provided here on this new directive, since it is only an amendment and the focus of this chapter is on the MDD and IVD MDD as already stated.

The **Breast Implant Reclassification Directive** (2003/12/EC) of 3 February 2003 is an amendment of the MDD (93/42/EEC) and is a brief document that reclassifies breast implants from Class IIb to Class III (Article 1). Breast implants placed on the market before September 1, 2003, were required to be reassessed as Class II devices before March 1, 2004. This means breast implants need to be manufactured within a full quality system and be subject to a review of the design dossier by a Notified Body. These measures have been applied by Member States since September 1, 2003.

NB: There has been intense discussion over recent years between the EU regulators and industry concerning the **Reclassification Directive Concerning Implantable Joints.** The European Commission confirmed, at the Medical Devices Experts Group (MDEG) meeting on December 14-15, 2004, that this is to be implemented despite protests from industry.

The reclassification will mean manufacturers of hip, knee and shoulder implants having to undergo a Notified Body (NB) review of their design dossier. There will be transitional arrangements to ensure Member States and manufacturers have time to implement these changes.

The **Animal Tissues Directive** (2003/32/EC) of 23 April 2003 introduced detailed specifications with respect to medical devices manufactured utilizing tissues of animal origin, and is an amendment of the MDD (93/42/EEC). The 'whereas' statements include

Products utilizing animal tissues are Class III, except "where such devices are intended to come in contact with intact skin only."

"(11) Annex I to Directive 93/42/EEC sets out the essential requirements that medical devices must meet pursuant to that Directive. Points 8.1 and 8.2 of that Annex set out specific requirements intended to eliminate or reduce as far as possible the risk of infection for the patient, user and third parties due to tissues of animal origin and specifies that the solutions adopted by the manufacturer in the design and construction of the devices must conform to safety principles taking into account the generally acknowledged state of the art."

"(12) With regard to medical devices manufactured utilizing tissues of animal origin it is necessary to adopt more detailed specifications in relation to the requirements of point 8.2 of Annex I to Directive 93/42/EEC and to specify certain aspects relating to the risk analysis and risk management in the framework of the conformity assessment procedures referred to in Article 11 of that Directive."

The Animal Tissues Directive defines various items such as cell, tissue, derivative, etc. and is concerned with minimizing the risks of transmitting transmissible spongiform encephalopathies (TSE) under normal conditions of use to patients or others. The animal tissues covered by the directive include bovine, ovine, caprine, deer, elk, mink and cats. Under Article 1 it is also stated that

"Collagen, gelatin and tallow used for the manufacturing of medical devices, shall meet at least the requirements as fit for human consumption."

Manufacturers need to note that they are required to justify why there is a need to use animal tissues or derivatives, and that third party suppliers must be audited. The 'Annex' of the Directive does provide clear indications of what is expected.

Holders of EC design-examination certificates or EC type-examination certificates issued before April 1, 2004 needed to apply for a complementary certificate "attesting to compliance with the specifications laid down in the Annex to this Directive". Until September 30, 2004, Member States had to accept the placing on the market and the putting into service of medical devices utilizing animal tissues that were covered by certificates issued before April 1, 2004. Clearly, all manufacturers of medical devices utilizing animal tissues must now fully comply with this Directive.

The following standards should be treated as de facto mandatory to consider and use as appropriate with medical devices utilizing tissues of animal origin:

- EN 12442-1:2000 Animal tissues and their derivatives utilized in the manufacture of medical devices. Analysis and management of risk.
- EN 12442-2:2000 Animal tissues and their derivatives utilized in the manufacture of medical devices. Controls on sourcing, collection and handling.
- EN 12442-3:2000 Animal tissues and their derivatives utilized in the manufacture of medical devices. Validation of the elimination and/or inactivation of viruses and transmissible agents.

Please note that this is a fast changing area and more changes are probable. Indeed, at the time this guide was being written, the European Commission's Medical Devices Experts Group (MDEG) was meeting (December 14-15, 2004) to discuss pragmatic issues concerning a number of medical devices utilizing animal tissues that are on the market but are not yet in full compliance with the new EU rules for these products, which came into force on October 1, 2004. At the meeting, it was agreed that regulators should accept, until April 30, 2005, devices on the market (to ensure the products are available) that may not be in full compliance with the new Directive 2003/32/EC. However, the devices concerned need to have been placed on the market before September 30, 2004 and the manufacturers must have sent their technical files addressing the new requirements to their NBs by December 31, 2004.

The **MDD** contains several recitals, 23 Articles and 12 Annexes. Annex I lists 14 essential requirements and the 54 subsets. Annexes II to VII describe six different routes to acquiring the CE marking. Annex VIII applies to custom-made devices. Annex IX outlines criteria for classifying medical devices. Annex X covers clinical evaluation. Annex XI describes the designation of Notified Bodies (NBs), and Annex XII illustrates how the CE marking should be applied. The MDD, including its annexes, is a key document and reference for those involved in implementing and maintaining quality assurance systems for medical device manufacturers.

The **IVD MDD** is very similar to the MDD in that it contains very similar language and structure to the MDD with several recitals, 24 Articles and 10 Annexes that cover much of the same effective content, especially from a quality systems standpoint, and therefore should now be familiar to most well-established medical device companies based in Canada, which export to

Europe, and especially for those already selling in compliance with the MDD or AIMD. Annex I lists 8 essential requirements, each with a number of subsets. ‘Annex II List of Devices Referred to in Article 9(2) and (3)’ gives in List A and List B literally a list of reagents, calibrators, controls and devices for the self-diagnosis of blood sugar considered to be higher-risk devices. ‘Annex III EC Declaration of Conformity’ matches with Annex VII of the MDD; ‘Annex IV EC Declaration of Conformity (Full Quality System)’ is the equivalent of MDD Annex II; ‘Annex V EC Type-Examination’ matches with MDD Annex III; ‘Annex VI EC Verification’ matches with MDD Annex IV; ‘Annex VII EC Declaration of Conformity (Production Quality Assurance)’ matches with the scope of MDD Annex V; ‘Annex VIII Statement and Procedures Concerning Devices for Performance Evaluation’ has no direct equivalent but does have parallels with MDD Annex VIII. ‘Annex IX Criteria for the Designation of Notified Bodies’ is very similar to MDD Annex XI and ‘Annex X CE Marking of Conformity’ is almost identical to MDD Annex XII as one would expect. The IVD MDD, including its annexes, is a key document and reference for those involved in implementing and maintaining quality assurance systems for *in vitro* medical device manufacturers.

1 Key Elements of the MDD and IVD MDD

1.1 Essential Requirements

Annex I of the MDD identifies 14 essential requirements plus a further 54 subsets that a manufacturer must satisfy before the CE marking can be placed on the product. Not all of these requirements are applicable to a single product. The essential requirements cover patient safety, product performance, safety in use, transportation and storage, risks and benefits, and design and construction requirements.

Annex I of the IVD MDD lists 8 essential requirements (ERs), each with a number of subsets, which has a very similar scope to that of the MDD. The IVD MDD does have some specifically IVD related requirements concerning confounding factors, reagent composition, analytical performance characteristics and self-testing devices.

1.2 Product Class

All medical devices are classified into four categories, as per the 18 classification rules contained in Annex IX of the MDD.

The IVD MDD effectively has four classifications of product: List A and List B devices (as referred to in Annex II of the Directive), self-test devices and all other devices roughly in descending order of risk.

1.3 Conformity Assessment Routes

Six conformity assessment routes to acquiring the CE marking are identified in Annexes II, III, IV, V, VI, and VII of the MDD.

Conformity assessment routes to acquiring the CE marking are identified in Annexes III, IV, V, VI, and VII of the IVD MDD. As with the MDD, there are typically two or even three different routes possible depending upon the device and quality system.

For manufacturers producing devices to any of the three main directives AIMD, MDD or IVD MDD and selling product into the US, it makes commercial sense to choose a conformity assessment route utilizing a full quality system, i.e., one with design controls. The US Food and Drug Administration (FDA) demands it for most Class II and all Class III devices, plus all devices that have software – including Class I devices. Both EN ISO 9001: 2000 and EN ISO 13485: 2003 quality standards require manufacturers to justify and document if they choose not to include design controls within their quality system. Use of EN ISO 13485: 2003 will typically

make for a better business, and this should be the primary consideration in choosing the appropriate form of quality system for a medical device manufacturer. EN ISO 13485: 2003 is consistent with FDA good manufacturing practices (GMP) and is the global quality standard for all forms of medical devices.

1.4 Technical Documentation

For both the MDD and IVD MDD, the technical documentation related to the quality system and/or the product is required, depending upon the product class and conformity assessment route followed. However, whatever route is followed, in practice the level of documentation completed is often similar to that for the full quality system approach recommended in the previous section.

1.5 Declaration of Conformity

A written declaration of conformity to the MDD or IVD MDD by the manufacturer is required prior to affixing the CE marking on the product.

1.6 Post-market Surveillance

For both the MDD and IVD MDD, the manufacturer is required to be proactive in monitoring post-production performance of the product.

The IVD MDD under ‘Article 12 European databank’ requires the creation of a European databank accessible to the competent authorities that hold data relating to registration of manufacturers; data on certifications issued, modified, supplemented, suspended, withdrawn or refused; data obtained from the vigilance procedure and all in a standardized format.

1.7 Vigilance Reporting

For both the MDD and IVD MDD, the manufacturer is required to establish and maintain a system for reporting and acting upon incidents affecting the health and/or safety of the patient or user or others. This includes incidents involving death or serious injury or those that might have led to such an outcome.

1.8 European Authorized Representative

The manufacturer with offices in Europe will normally choose to be their own 'authorized representative,' although they can choose an alternative. Article 10 of the IVD MDD states "Where a manufacturer who places on the market under his own name does not have a registered place of business in a Member State, he shall designate an authorized representative." The authorized representative has to inform the competent authority of the member state where they are located and provide contact details.

Note the IVD MDD modifies the MDD and defines an authorized representative as

"…any natural or legal person established in the Community who, explicitly designated by the manufacturer, acts and may be addressed by authorities and bodies in the Community instead of the manufacturer with regard to the latter's obligations under this Directive."

2 Six Steps to Acquiring the CE Marking under the MDD

2.1 Classify Your Product

The MDD classifies medical devices into four classes (I, IIa, IIb and III). Classes range from the lowest risk and hence least stringent (Class I) to the higher risk, most stringent (Class III). Section 3.1 of this guide provides guidance on how to determine the product class.

2.2 Select the Best Conformity Assessment Route

The conformity assessment routes available to the manufacturer are determined by the class of the product. The six conformity assessment routes are applied in different combinations, depending upon the product. Product Class I offers two routes, Class IIa and Class IIb offer four routes and Class III offers three routes. Each of the six routes is described fully in Annexes II to VII of the MDD. Their application for particular product classes is illustrated in Figures 1 to 4 of this chapter. Custom-made devices and devices intended for clinical evaluation are covered under Annexes VIII and X, respectively and are not allowed to carry the CE marking.

2.3 Apply for Registration

Each EU Member State appoints a Competent Authority (CA) to act as the State's regulator and the CA in turn appoints Notified Bodies (NBs) to implement the requirements of the directives in regard to certification of manufacturers' CE marking and quality systems. Manufacturers need to register with a CA. NBs are typically test laboratories and quality systems houses that audit quality systems of medical device companies and test their products for compliance with applicable standards. NB certification is required for compliance with the MDD for Class I devices with a measuring function or sterile packaging function, and all Class IIa, Class IIb and Class III devices. Manufacturers can self-certify for Class I devices without a measuring function or sterile packaging.

Contact information on all Competent Authorities is available via

http://europa.eu.int/comm/enterprise/medical_devices/ca/list_ca.htm

and all Notified Bodies available via

http://europa.eu.int/comm/enterprise/newapproach/legislation/nb/notified_bodies.htm

MEDDEV 2.12-1 rev 4 (April 2001) Guidelines on a Medical Devices Vigilance System is available from

http://europa.eu.int/comm/enterprise/medical_devices/meddev/2_12-1___04-2001.pdf

European CAs for the national vigilance systems are provided in the 'List of vigilance contact points within the National/Competent Authorities', which is available on the web at http://europa.eu.int/comm/enterprise/medical_devices/ca/ca_vig.htm

Note the IVD MDD modifies the MDD:

This requirement also has relevance to the MDD and is modified via the IVD MDD under 'Article 21 Amendment of directives.' This section of the IVD MDD lists a number of modifications to the MDD in regard to definitions, the European databank and particular health monitoring measures. It is thus important for all medical device manufacturers to read this section, since after a long delay the European Databank is being implemented across Europe. It is an important issue to discuss with your chosen Notified Body (NB) and your Authorized Representative (if you use one); hence, the next section has been included to be informative.

European Databank and Global Medical Device Nomenclature System (GMDN)

This is another item that is evidence of the global convergence of medical device regulation and is a system for providing common descriptions of medical devices. It is currently being implemented across Europe but each country's implementation timetable is different in detail. The GMDN nomenclature will be used for registering medical devices and exchanging information about them around the world, especially for vigilance issues. Much more background is available at the GMDN web site www.gmdn.org and the following quote is taken from this site:

"What is the GMDN?

The Global Medical Device Nomenclature (GMDN) is a collection of internationally recognized terms used to accurately describe and catalogue medical devices. In particular, the products used in the diagnosis, prevention, monitoring, treatment or alleviation of disease or injury in humans.

Medical Device experts from around the world (manufacturers, healthcare authorities and regulators) compiled the GMDN, which has taken almost 4 years of international consultation and discussion. It contains nearly 7,000 terms plus more than 10,000 synonyms to make the GMDN easier to use.

The GMDN is a classification system developed to allow for the classification of all Medical Devices put onto the market as defined in the three European Directives.

Currently, the GMDN is divided into 12 Categories of devices to encompass all of these products. As new product areas need to be included into this classification system, a new Category code will be allotted and that Category developed. The next hierarchical level of the system is the Generic Device Group; this is the actual nomenclature level or the naming level, by which a product, or group of similar products, can be classified using a selected generic descriptor and its unique code. For information about the full GMDN structure you can download the GMDN User Guide from this site."

Once the pan-European systems are complete, Competent Authorities (CAs) will want manufacturers to register using the GMDN codes and typically, this will require a fee. The licence for using the GMDN database is in Euros: 500 for less than 2 employees; 1,500 for 2 to 10 employees; 2000 for 10-100 employees and 2,500 for more than 100 employees.

The guides available at the web site do have examples in them and a glossary of terms.

2.4 Provide Technical Documentation

Technical documentation is examined by the NB and must demonstrate that the quality system and/or product complies with the requirements of the MDD. Quality system compliance or product compliance, or both, might be required depending upon the conformity assessment route chosen. Some Competent Authorities (CAs) do undertake sample audits of Class I technical documentation to ensure it is correct and as a check on the self-certifying process.

a) Where quality system compliance is required, evidence must be provided in the form of quality system documentation such as policies, procedures, work instructions and records.

b) Where product compliance is required, evidence must be provided to demonstrate that the product's design, manufacture and performance meet the essential requirements of the MDD. This evidence must include specific technical information, stipulated in the appropriate Annex of the MDD, to which the product will be certified.

2.5 Make Declaration of Conformity

When a manufacturer is satisfied that a product meets all of the applicable essential requirements (ERs), a declaration of conformity covering the product is written. It is illegal (a criminal offence) for a manufacturer (an individual named person signs the form) to provide false or misleading information on a declaration of conformity.

2.6 Affix the CE Marking

After the declaration of conformity is written, a manufacturer can affix the CE marking on the product. It is important to wait for written confirmation from the NB, if not a self-certifying Class I device, before placing the device on the market, and this typically occurs several weeks after the certification audit, allowing time for internal checking by the NB to be completed.

3 What Each Step Involves

3.1 Classifying Your Product

The manufacturer must first determine if the device is a medical device. The MDD definition of a medical device is contained in the Glossary of the present guide. Medical devices are classified according to their intended use. Annex IX of the MDD contains the 18 rules for classifying devices. These rules are applied to help a manufacturer determine whether the device is Class I (low risk), Class IIa (medium risk), or Classes IIb or III (high risk). The 18 rules cover various combinations of the following criteria:

- duration that the device is in contact with the patient (i.e., transient, short or long term);
- whether it is invasive or non-invasive (e.g., it involves blood filtration or contact with the skin);
- degree of invasiveness (e.g., whether it involves a body orifice or is surgically implantable);
- anatomy affected by the device (e.g., central nervous system);
- active or non-active (i.e., powered or non-powered); and
- special situations (e.g., devices incorporating a medicinal substance or utilizing animal tissue, contact lens solutions).

Where multiple uses are claimed, or where more than one rule could apply, the highest classification rule applies.

The classification process can be complex and is dependent upon the interpretation of each rule as applied to a given device. The manufacturer is responsible for determining which rules apply to the product and for its classification. It is important that this be done early in the process as it determines the conformity assessment routes available for that product and the technical documentation required. Engaging the services of the chosen NB early in the process assists manufacturers to verify the appropriate device class.

'MEDDEV 2.4/1 Rev.8 (July 2001) Guidelines to the Classification of Medical Devices' does not have legal status but is the most comprehensive guide to EU medical device classification. It is available with all other MEDDEVs from
http://europa.eu.int/comm/enterprise/medical_devices/meddev/index.htm

3.2 Choosing the Conformity Assessment Route

Each device class offers different conformity assessment routes to acquiring the CE mark. These routes are illustrated in Figures 1 to 4. Each device class uses a combination of the routes described in Annexes II, III, IV, V, VI and VII of the MDD.

For Class I devices, Annex VII must be applied. For Class IIa devices, Annex II (excluding Section 4) can be applied alone, or Annex VII can be applied in combination with Annex IV or V or VI.

For Class IIb devices, Annex II (excluding Section 4) can be applied alone or Annex III can be applied in combination with Annex IV or V or VI.

For Class III devices, Annex II (including Section 4: design dossier) can be applied alone, or in combination with Annex IV or V.

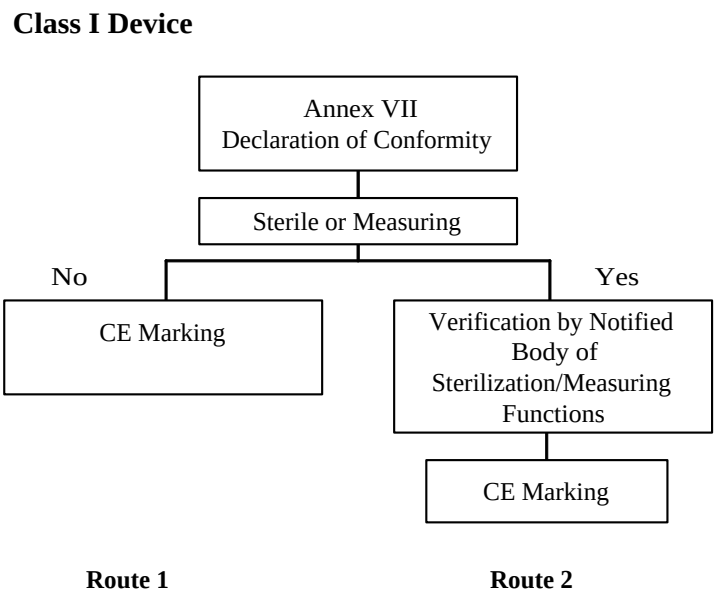

Figure 1: Conformity Assessment Route - Class I Devices

3.2.1 Class I Device

Route 1: Application of Annex VII for products with no sterile or measuring functions

> Manufacturer makes written declaration of conformity, stating that the product complies with the MDD and affixes the CE marking (Section 1, Annex VII).

Manufacturer provides technical documentation to demonstrate the product's compliance with the MDD and makes this available, along with declaration of conformity, to national authorities, upon request, up to five years after the last of that product has been manufactured (Section 2, Annex VII).

Manufacturer institutes procedures to undertake post-market surveillance and vigilance reporting to national authorities (Section 4, Annex VII).

Route 2: Application of Annex VII for products with sterile or measuring functions

All of the steps for Route 1, plus

NB verifies that the sterilization and/or the measuring function of the product complies with the MDD (Section 5, Annex VII).

3.2.2 Class IIa Device

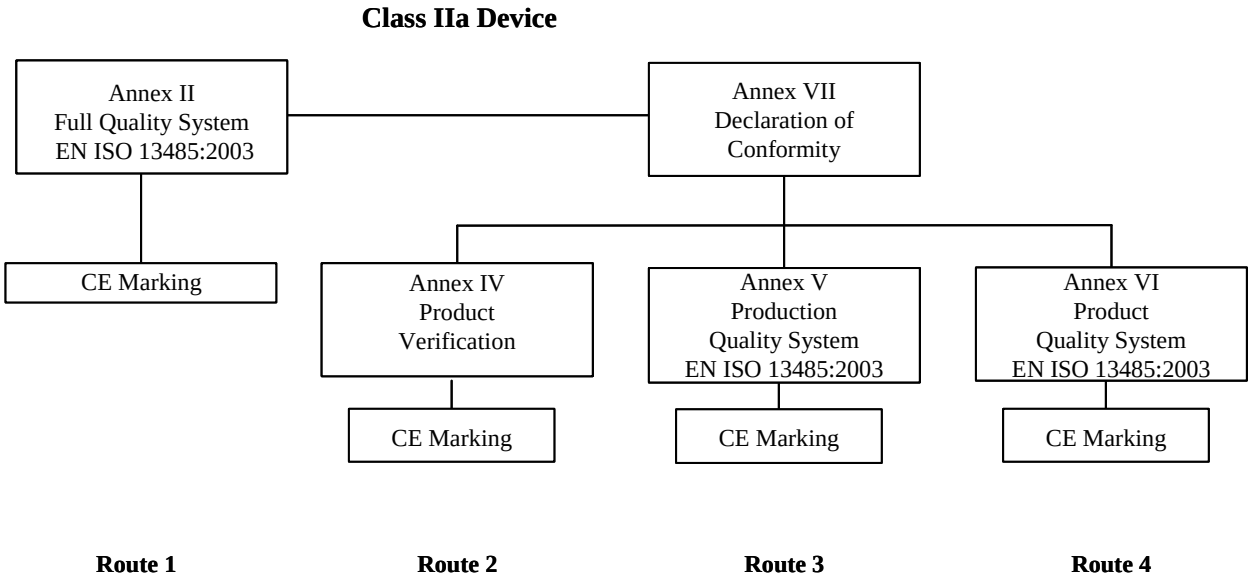

Figure 2: Conformity Assessment Route - Class IIa Devices

Route 1: Application of Annex II (excluding Section 4)

NB approves quality system to Annex II of the MDD, using EN ISO 13485: 2003 (Annex II, Section 4 'Examination of the design of the product' is not applicable.)

Manufacturer makes written declaration of conformity and affixes CE marking.

Manufacturer institutes procedures to undertake post-market surveillance and vigilance reporting to national authorities (Section 3.1, Annex II).

Route 2: Application of Annex VII with Annex IV

Manufacturer provides technical documentation to demonstrate the product's compliance with the MDD (Section 2, Annex VII).

NB examines/tests each individual product or sample to verify conformity to technical documentation referred to above (Section 4, Annex IV).

NB affixes its identification number to the approved product and creates a certificate of conformity for the product (Section 5.2, Annex IV).

Manufacturer declares that the product complies with the technical documentation referred to above and in the MDD (Section 8.1, Annex IV).

Manufacturer institutes procedures to undertake post-market surveillance and vigilance reporting to national authorities (Section 3, Annex IV).

Route 3: Application of Annex VII with Annex V

Manufacturer provides technical documentation to demonstrate the product's compliance with the MDD (Section 2, Annex VII).

NB approves quality system to Annex V of the MDD, using EN ISO 13485: 2003, including any justified exemption from product realization (Section 1, Annex V).

Manufacturer makes written declaration of conformity and affixes CE mark (Section 2, Annex V).

Manufacturer institutes procedures to undertake post-market surveillance and vigilance reporting to national authorities (Section 3.1, Annex V).

Route 4: Application of Annex VII with Annex VI

Manufacturer provides technical documentation to demonstrate the product's compliance with the MDD (Section 2, Annex VII).

NB approves quality system to Annex VI of the MDD, using EN ISO 13485: 2003, including any justified exemption from product realization (Section 1, Annex VI).

Manufacturer makes written declaration of conformity and affixes CE marking (Section 2, Annex VI).

Manufacturer institutes procedures to undertake post-market surveillance and vigilance reporting to national authorities (Section 3.1, Annex VI).

3.2.3 Class IIb Device

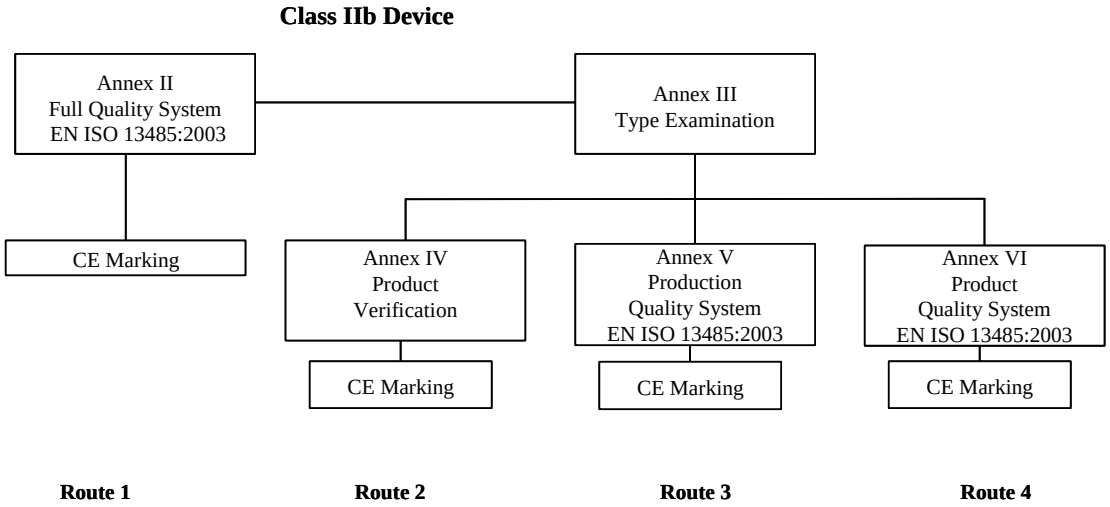

Figure 3: Conformity Assessment Route - Class IIb Devices

Route 1: Application of Annex II (excluding Section 4)

This is the same as in Route 1 for Class IIa devices.

Route 2: Application of Annex III with Annex IV

Manufacturer submits to NB a representative sample of product, or 'type,' along with supporting technical documentation, to assess compliance of type with MDD (Section 2, Annex III).

NB examines type and verifies that it was manufactured in conformity to technical documentation; conducts tests to assess compliance of type with MDD; and issues an EC type examination certificate (Sections 4 & 5, Annex III).

Manufacturer ensures the product conforms to the type approved in the EC type examination certificate; writes declaration of conformity; and affixes the CE marking (Section 2, Annex IV).

NB examines/tests each individual product or sample to verify conformity to type approved in EC type examination certificate and the MDD (Section 5.1, Annex IV).

NB affixes its identification number to products approved and draws up certificate of conformity for these products (Section 5.2, Annex IV).

Manufacturer institutes procedures to undertake post-market surveillance and vigilance reporting to national authorities (Section 3, Annex IV).

Route 3: Application of Annex III with Annex V

Manufacturer submits to the Notified Body a representative sample of product, or 'type,' along with the supporting technical documentation, to assess compliance of type with MDD (Section 2, Annex III).

NB examines type and verifies that it was manufactured in conformity to technical documentation; conducts tests to assess compliance of type with MDD; and issues an EC type examination certificate (Sections 4 & 5, Annex III).

NB approves quality system to Annex V of the MDD, using EN ISO 13485: 2003, including any justified exemption from product realization (Section 1, Annex V).

Manufacturer makes written declaration of conformity and affixes CE marking (Section 2, Annex V).

Manufacturer institutes procedures to undertake post-market surveillance and vigilance reporting to national authorities (Section 3.1, Annex V).

Route 4: Application of Annex III with Annex VI

Manufacturer submits representative sample of product, or 'type,' along with supporting technical documentation to Notified Body to assess compliance of type with MDD (Section 2, Annex III).

NB examines type and verifies that it was manufactured in conformity to technical documentation; conducts tests to assess compliance of type with MDD; and issues an EC type examination certificate (Sections 4 & 5, Annex III).

NB approves quality system to Annex VI of the MDD, using EN ISO 13485: 2003, including any justified exemption from product realization (Section 1, Annex VI).

Manufacturer makes written declaration of conformity and affixes CE marking (Section 2, Annex VI).

Manufacturer institutes procedures to undertake post-market surveillance and vigilance reporting to national authorities (Section 3.1, Annex VI).

3.2.4 Class III Device

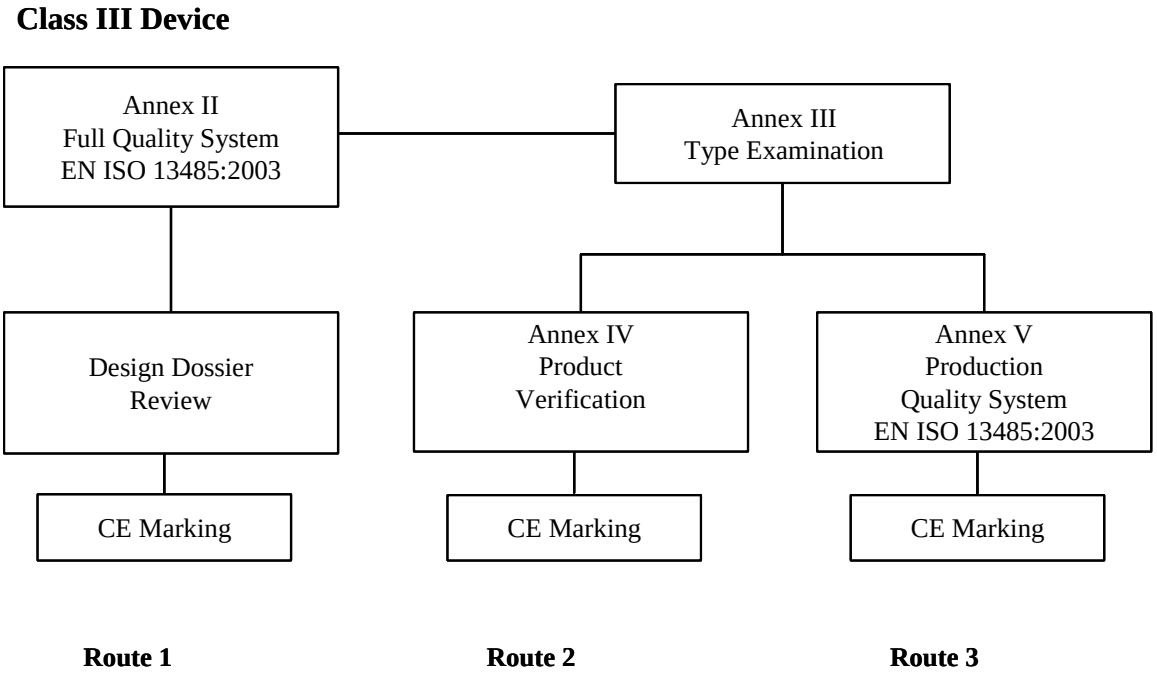

Figure 4: Conformity Assessment Route - Class III Devices

Route 1: Application of Annex II, including Section 4, examination of design dossier

NB approves quality system to Annex II of the MDD, using EN ISO 13485: 2003 in full (Section 1, Annex II).

NB examines technical documentation related to product design, manufacture and performance (design dossier) to assess compliance with MDD and issues an EC design examination certificate (Section 4, Annex II).

Manufacturer makes written declaration of conformity and affixes CE marking (Section 2, Annex II).

Manufacturer institutes procedures to undertake post-market surveillance and vigilance reporting to national authorities (Section 3.1, Annex II).

Route 2: Application of Annex III with Annex IV

Same as Route 2 for Class IIb devices

Route 3: Application of Annex III with Annex V

Same as Route 3 for Class IIb devices

3.3 The Registration Process

3.3.1 Selecting a Notified Body

The registration, or audit, process is similar to that for ISO 9000 registration. Only European accredited NBs are permitted to certify a quality system or device as fit for the CE marking. Some European-based NBs are affiliated with Canadian-based ISO 9000 registrars. There are advantages in working with European NBs that have such affiliations because some NBs will permit the Canadian affiliate to conduct part of the audit and submit the findings to the NB for approval, thereby avoiding the need for a second auditor to travel from Europe.

Some Canadian registrars advertise memoranda of understanding with NBs. In selecting an NB, the manufacturer must carefully enquire about such agreements. When considering a Canadian registrar that has some form of NB affiliation, a manufacturer should direct very specific questions about how the process works and, in particular, what certificates will be provided, by what body, by whom these will be recognized and the likely time frames involved at each stage.

3.3.2 The Process

Information Sessions: Some NBs offer a free information session but bill for travel costs. These sessions are intended to describe the registration process and to answer questions. They are not mandatory.

Pre-Audit: NBs usually offer pre-audits, which serve to evaluate the feasibility of a successful certification audit. NBs charge for this service, usually two days plus travel. Again, this service is not mandatory but is recommended.

Document Review: The NB reviews the company's quality system documentation, including the quality manual (policies, organizational structure, etc.) and procedures manual. This is mandatory.

Certification Audit: The NB conducts an on-site audit. The audit team typically consists of a lead auditor and an auditor with expertise in the product or products being manufactured. The number of auditors corresponds to the size of the organization being audited. One auditor must represent an EU notified body. Following a successful audit, the lead auditor will recommend to their NB that the organization receive its certification. If nonconformities are observed, a follow-up audit may be required. Sometimes only a paper review of the corrective actions is performed, and the implementation is checked during a subsequent surveillance audit. Once the CE marking is acquired, it normally lasts five years. Continued compliance after the audit is verified by NBs through surveillance audits. This process is mandatory.

Surveillance Audit: The NB conducts periodic audits of all or parts of the quality system to ensure that the company can maintain its certification. Audit frequency is usually every six months or once annually. Surveillance audits are mandatory.

Certificate of Registration: The certificate of registration is issued four to six weeks after the lead auditor recommends certification. The total certification process can take from three to six months.

Design Dossier or Type Examination Review: In addition to the quality system certification, the NB must review the technical files in support of an EC design examination certificate for Class III devices. The technical files in support of the EC design examination certificate are called a design dossier. As an alternative to a design dossier review, a manufacturer may choose to have a product specimen or 'type' tested by an NB to verify product conformance to the essential requirements of the MDD. When the specimen or type is approved, the NB will issue an EC type examination certificate. The EC design examination certificate or the EC type examination certificate, plus the quality system approval, permit the manufacturer to declare conformity to the MDD and to affix the CE marking to Class III products. The type testing route is also possible for Class IIb devices (see figure 3).

3.3.3 Registration Cost

The cost of registration depends on

- the size of the company being registered;
- the class of product and whether type examinations or design dossier reviews are required;
- the number of different products manufactured and their complexity; and
- whether subcontractors have to be visited by the auditors.

NBs charge for the documentation review process; on-site audits; reviews of design dossiers where appropriate (Class III devices); type examination tests where appropriate (Class IIb or III devices); semi-annual or annual surveillance audits; administrative fees; and travel costs. On the basis of sample information received from some NBs, it is reasonable to assume that a manufacturer in the size range of 30 employees, manufacturing a Class III device and requiring a design dossier review, would be required to pay in the range of $25,000 to $30,000 Canadian. This cost estimate includes travel and semi-annual or annual surveillance audits for three years. Where there is no requirement for a design dossier review or a type examination test, this cost would typically be in the range of $17,000 to $22,000 Canadian.

If an NB or a participating Canadian registrar is requested to also issue a quality system certificate pertaining to EN ISO 13485, a relatively small additional cost may be charged.

Manufacturers are encouraged to shop around for NBs that offer the best price and certificates that provide the broadest recognition. Manufacturers are also encouraged to negotiate for additional quality system certificates at no or little extra cost. Manufacturers should submit questionnaires to five or more NBs, listing the criteria upon which they will be selected. A sample questionnaire is attached as Appendix 2. It is also important to select an NB early in the process, as the NB’s input on device class, scope of registration, etc., will be extremely valuable in defining the registration cost and planning the implementation process. A pre-audit assessment by an NB is usually very instructive and could cost another $3,000 including travel.

3.4 Technical Documentation

The NB must examine and approve technical documentation related to the quality system and/or product before a manufacturer can affix the CE marking to the product. The type of technical documentation required depends upon the product class and the conformity assessment route being followed. For example, to affix the CE marking to a Class III device, the manufacturer must receive from an NB two certificates:

a) Certificate registering the quality system; and

b) Certificate demonstrating that the product meets the safety, health, environment and consumer protection requirements of the MDD.

3.4.1 Quality System Documentation

Technical documentation, in support of a quality system registration, is required when a manufacturer of Class III devices chooses to follow Routes 1 and 3. Where a manufacturer of Class IIa or IIb devices chooses to follow Routes 1, 3, and 4 for each of those classes, supporting technical documentation is likewise required for quality system registration.

A quality system to EN ISO 13485: 2003 is recommended for all medical device manufacturers. Please see the Introduction and Quality System Overview for more details.

The MDD requires quality systems to be registered to a particular Annex of the MDD, not to a particular standard. However, NBs now expect all manufacturers placing medical devices on the European market to be using EN ISO 13485: 2003.

3.4.2 Product Documentation

Technical documentation is also required to support product compliance with the MDD for specific device classes and conformity routes: The higher the device class, the more stringent the requirements for product documentation. Class III devices require an EC design examination certificate, supported by a design dossier, or an EC type examination certificate, depending upon the conformity route followed. Technical documentation in support of an EC type examination certificate is described in Section 3, Annex III of the MDD and is listed in Section 3.4.2.2 below. Class IIb devices following Routes 2, 3, or 4 also require an EC type examination certificate. For Class IIa devices, technical documentation in support of a declaration of conformity (Annex VII) is required if Routes 2, 3 or 4 are followed.

3.4.2.1 The Design Dossier

A design dossier is required only for a Class III device. A design dossier describes the design, manufacture and performance of the product in question. It must include all the documents needed to assess whether the product conforms to the applicable essential requirements of the MDD. In essence, the manufacturer requires evidence to demonstrate compliance when the conformity of the product is assessed. Examples of evidence for a typical Class III device include some or all of the specifications, manufacturing processes, labels, literature (including instructions for use and any warnings or precautions), together with the results of a risk analysis, design and development testing, clinical investigation, reports from use of the product or similar experience, quality control tests and other product-related documents. This evidence is usually contained in reports ("primary reports") on the topics mentioned above, which are held by the manufacturer and sometimes by others, such as subcontractors. These documents are often kept in the files of different departments that handle the relevant subject matter, and there is no requirement that all the documentation be kept in one place. A design dossier generally aligns with the US FDA's Design History File.

EUCOMED (European Confederation of Medical Devices Associations) has developed a suggested list of technical documentation that a manufacturer should compile to complete a design dossier for a given product or product group. This list is outlined in Appendix 3 of the present guide.

3.4.2.1.1 Approach to Developing a Design Dossier

A separate design dossier is required for each product or product group where similar products make up a product group. The manufacturer determines which products constitute a similar product group. The criteria for grouping products are usually 1) the same material used; 2) the same intended use; and 3) the same manufacturing process.

The first step in preparing a design dossier is to determine the number of products or product groups. The second step is to identify which of the essential requirements (ERs) apply to each product group. The third step is to complete an ER checklist for each product group and, if an ER applies, reference evidence of compliance. It is up to the manufacturer to decide what measures constitute sufficient or appropriate compliance. If an ER does not apply, the manufacturer should indicate that it is not applicable.

The MDD does not specify any procedural requirements regarding how a manufacturer must demonstrate that its product meets the applicable ERs. There is no specified format or documentation required to demonstrate compliance. EUCOMED has developed a checklist that it recommends for this purpose. This checklist, contained in Appendix 4 of the present guide, can be used to briefly summarize the basis on which a product group meets the ERs (e.g., reference to a harmonized standard or to a specific technical report or file). Often, a table is created containing the ERs, the measures taken to address each ER and references to supporting technical documentation.

An Essential Requirements Checklist is recommended for every product group.

Relevant documents such as technical files, work instructions and procedures are referenced as primary technical documents. These technical documents referenced in the ER checklist, including reviews of customer complaints, draft labels, and quality system certificates, constitute the design dossier for this particular product. The design dossier must be submitted to the NB along with the ER checklist. The design dossier is returned to the manufacturer after it has been reviewed by the NB.

Where the term "well-established product" is used, NBs require scientific evidence. This evidence might include analysis of all customer complaints, adverse incidents, number of design changes with a critique/analysis and a trend analysis of key parameters to show the device is under demonstrable control within an established quality system. Reliance on the term "a well-established product" is not recommended for a Class III device. As stated in 'Annex X Clinical Evaluation,' "as a general rule," compliance with ERs of Sections 1 and 3 of Annex I "must be based on clinical data in particular in the case of implantable devices and devices in Class III. Taking account of any relevant harmonized standards…." The 'Methods' of Section 2.3 of Annex X are clearly dependent on sound scientific validity, clinical investigations under normal use and a written report. Clinical investigations have to be notified to the CA (see Article 15).

Where compliance can be shown with a harmonized standard, the NB must accept that this meets the requirements of the directive for the scope of that harmonized standard.

The manufacturer must inform the NB of any significant changes to the approved product; the NB's approval of such changes is typically in the form of a supplement to the initial EC design examination certificate. The manufacturer or its authorized representative must keep a copy of the relevant certificate(s) and their additions for at least five years after the last device has been manufactured.

3.4.2.2 Type Examination

The manufacturer must submit to the NB a product specimen or 'type,' along with supporting technical documentation, to ascertain conformity to the ERs of the MDD. Sufficient technical documentation must be provided to allow the NB to understand the design, manufacture and performance of the product. The technical documentation must contain the following items:

A general description of the 'type,' including any variants planned;

Design drawings, methods of manufacture envisaged, in particular as regards sterilization, and diagrams of components, subassemblies, circuits, etc.;

The descriptions and explanations necessary to understand the above;

A list of the harmonized standards which have been applied or a description of the solutions adopted to meet the ERs of the MDD. Harmonized standards are listed in the *Official Journal of the European Communities,* and this list is available via the EC web site mentioned earlier or via http://europa.eu.int/comm/enterprise/newapproach/standardization/harmstds/whatsnew.html.

Results of relevant design calculations, risk analysis, investigations, technical tests, etcetera;

A statement indicating whether or not the device incorporates, as an integral part, a substance which, if used separately, may be considered a medicinal product (ref: Section 7.4 of Annex I of the MDD);

Clinical data referred to in Annex X of the MDD;

A draft label; and

The appropriate instructions for use, as required.

Where a declaration of conformity was followed as per Annex VII, the following technical documentation, in addition to the above, shall be provided:

(for products placed on the market in a sterile condition) a description of the methods used for sterilization;

(if the device is to be connected to (an)other device(s) in order to operate as intended) proof that it conforms to the essential requirements when connected to any such device(s).

An NB issues an EC type examination certificate after a review of the technical documentation confirms that the 'type' conforms to the MDD. The manufacturer then prepares a declaration of conformity, indicating that a particular product or number of products conform to the approved 'type' and satisfy the ERs of the MDD. The manufacturer must take all of the necessary measures to ensure that the products conform to the 'type' approved in the EC type examination certificate. That the manufacturer has done so is verified by the NB through end product testing. This testing can be conducted on individual products or on product batches. Where the end products or batches conform to the EC type examination certificate, the NB issues a certificate of conformity related to the tests conducted. In the case of Class IIa products, where no type examination is involved, the NB examines end products to determine whether they conform to the technical documentation submitted as part of the Annex VII conformity route.

The manufacturer must inform the NB of any significant changes to the approved product and the NB's approval of such changes is in the form of a supplement to the initial EC type examination certificate. The manufacturer or its authorized representative must keep a copy of the relevant certificate(s) and their additions for at least five years after the last device has been manufactured.

3.4.3 Location of Technical Documentation

The MDD requires that technical documentation be maintained and made available to national authorities upon request. European Commission guidelines suggest that, for non-European-based manufacturers, only a summary technical file needs to be kept within the EU. This summary file would be kept by the manufacturer's designated representative within the EU and consist of the following:

Name and address of the manufacturer and identification of the product;

A list of harmonized standards and/or the solutions adopted to satisfy the essential requirements of the MDD (ER checklist);

A product description;

The product's operating instructions, if any; and

a product plan, if any.

In addition to this, many Notified Bodies suggest that copies of quality system and product approvals be kept with the summary file in Europe.

The European Commission suggests that the detailed file, consisting of tests, reports, quality manual, procedures manual, detailed product descriptions and specifications, etc., be kept with the manufacturer. Specific detailed files would have to be made available to national authorities, upon request, within a reasonable period.

3.5 Declaration of Conformity

A declaration of conformity is the process whereby the manufacturer ensures and declares that the product intended for the EU market meets the applicable provisions of the MDD. A declaration of conformity has legal status within the EU, and any manufacturer making false claims through the issue of a declaration of conformity could be liable.

Declarations of conformity are written. How the manufacturer chooses to document the declaration of conformity depends upon the manufacturer's product line and volume. For a single product, the manufacturer may choose to write a separate declaration for each product. The manufacturer placing several products on the market may wish to write a blanket declaration listing all the product lines that are covered by the declaration.

3.6 Affixing the CE Marking

Since June 14, 1998, all medical devices sold within the EU must display the CE marking on the product or its sterile pack, where practical, and on the instructions for use. Custom-made medical devices and those intended for clinical investigation are not to display the CE marking although they must comply with virtually all the ERs.

For Class I devices that do not incorporate sterilization or measuring functions, the manufacturer can 'self-declare' that the product meets the essential requirements of the MDD and affix the CE marking without the interventions of an NB. For Class I devices incorporating a sterilization or measuring function, the intervention of an NB is required to assess the sterilization and/or measuring functions only. Since only either or both of these two functions have been assessed by the NB, the CE marking does not include the NB number. For Class IIa, IIb and III devices, the intervention of an NB is required. For these classes, the NB verifies that the device meets the essential requirements of the MDD. When satisfied that the device meets the MDD requirements, the NB issues the appropriate certificates related to product compliance, and/or quality system compliance, depending upon the device class and conformity route chosen. For example, a Class III product would have an EC design examination certificate plus a quality systems certification to Annex II of the MDD, or an EC type examination certificate plus a quality systems certification to Annex V of the MDD. Once these certificates are provided, the manufacturer writes a declaration of conformity and affixes the CE marking.

For Class IIa, IIb and III devices, the CE marking must be followed by the identification number of the NB issuing the certificates.

Manufacturers, or their authorized representatives within the EU, are responsible for affixing the CE marking. EU member states can have a manufacturer's product withdrawn from the market where the CE marking has been unduly affixed or provides misleading information. Annex XII of the MDD specifies how the CE marking must be applied.

4 Six Steps to Acquiring the CE Marking under IVD MDD

4.1 Classify Your Product

The IVD MDD classifies IVDs into four broad categories from relatively low-risk to high-risk devices. These are

- Other devices, i.e., not Annex II or self-testing devices.
- Self-testing devices, except those for blood sugar.
- Annex II List B, which includes tests for chlamydia, phenylketonuria, rubella, toxoplasmosis and self-test products for blood sugar.
- Annex II List A, covering tests for blood grouping and infections such as HIV and hepatitis.

The full list of List A and B products is included in the IVD MDD.

4.2 Select the Best Conformity Assessment Route

The conformity assessment routes available to the manufacturer are determined by the classification of the product and choice of the manufacturer. As with the MDD, the IVD MDD conformity assessment routes are applied in different combinations, depending upon the product. 'Other Devices' has a light touch approach, like Class I of the MDD, and requires only a declaration of conformity to Annex III, unless the IVD is for performance evaluation; then Annex VIII applies. The other IVD categories are broadly similar to the process under the MDD and will be readily understood by those familiar with this process. The choices comprise a full quality system or combination of a declaration of conformity and type examination, or product/production verification, or examination of design.

Each of the routes is described fully in Annexes III to VII of the IVD MDD. Their application for particular product category is illustrated in Figures 5 to 8 of this chapter. Devices intended for performance evaluation are covered under Annex VIII. These do not require the CE marking and are the equivalent of devices undergoing clinical evaluation of the MDD.

4.3 Apply for Registration

Each EU Member State appoints a Competent Authority (CA) to act as the State's regulator and the CA in turn appoints Notified Bodies (NBs) to implement the requirements of the directive in regard to certification of manufacturers' CE marking and quality systems. This is the same process as that for the MDD.

Contact information on all Competent Authorities is available via
http://europa.eu.int/comm/enterprise/medical_devices/ca/list_ca.htm

and all Notified Bodies available via
http://europa.eu.int/comm/enterprise/newapproach/legislation/nb/notified_bodies.htm

MEDDEV 2.12-1 rev 4 (April 2001) Guidelines on a Medical Devices Vigilance System is available from
http://europa.eu.int/comm/enterprise/medical_devices/meddev/2_12-1___04-2001.pdf

European CAs for the national vigilance systems are provided in the 'List of vigilance contact points within the National/Competent Authorities', which is available on the web at
http://europa.eu.int/comm/enterprise/medical_devices/ca/ca_vig.htm

Note the IVD MDD modifies the MDD:

This requirement also has relevance to the MDD and is modified via the IVD MDD under 'Article 21 Amendment of directives.' This section of the IVD MDD lists a number of modifications to the MDD in regard to definitions, the European databank and particular health monitoring measures. It is thus important for all medical device manufacturers to read this section, since after a long delay the European Databank is being implemented across Europe. It is an important issue to discuss with your chosen Notified Body (NB) and your Authorized Representative (if you use one).

Please see the earlier MDD section that discussed the **European Databank and Global Medical Device Nomenclature System (GMDN)** and applies equally to IVDs.

4.4 Provide Technical Documentation

As with the MDD, the IVD MDD technical documentation is examined by the NB(s) and must, therefore, demonstrate that the quality system and/or product complies with the requirements of the MDD. Quality system compliance or product compliance, or both, might be required depending upon the conformity assessment route chosen.

a) Where quality system compliance is required, evidence must be provided in the form of quality system documentation such as policies, procedures, work instructions and records.

b) Where product compliance is required, evidence must be provided to demonstrate that the product's design, manufacture and performance meet the essential requirements of the IVD MDD. This evidence must include specific technical information, stipulated in the appropriate Annex of the IVD MDD to which the product will be certified.

4.5 Make Declaration of Conformity

When a manufacturer is satisfied that a product meets all of the applicable essential requirements, a declaration of conformity covering the product is written. It is illegal for a manufacturer (an individual named person) to provide false or misleading information on a declaration of conformity.

4.6 Affix the CE Marking

After the declaration of conformity is written, a manufacturer can affix the CE marking on the product. It is important to wait for written confirmation from the NB, if not a self-certifying device, before placing the device on the market, and this is typically several weeks after the certification audit, allowing time for internal checking by the NB to be completed.

5 What Each Step Involves

5.1 Classifying Your IVD

The manufacturer must first determine if the device is an IVD medical device. The IVD MDD definition of an 'in vitro diagnostic medical device' is contained in the IVD MDD under 'Article 1 Scope, definitions'. Classifying an IVD is then simply ensuring it is put into one of the broad categories mentioned earlier:

- Other devices, i.e., not Annex II or self-testing devices.
- Self-testing devices, except those for blood sugar.
- Annex II List B, which includes tests for chlamydia, phenylketonuria, rubella, toxoplasmosis and self-test products for blood sugar.
- Annex II List A, covering tests for blood grouping and infections such as HIV and hepatitis.

There are no classification rules for IVDs. Where there is any doubt, it is recommended the manufacturer discuss this with the chosen NB. Also, it is strongly recommended that all IVD manufacturers, wherever they have European offices, read the UK's MHRA guidance notes available at
http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodeId=369

- Guidance Notes for the Registration of Person Responsible for Placing *In-Vitro* Diagnostic Medical Devices on the Market; and
- Guidance Notes on In Vitro Diagnostic Medical Devices Directive 98/79/EC.

5.2 Choosing the Conformity Assessment Route

Each of the four categories offers different conformity assessment routes to acquiring the CE marking. These routes are illustrated in Figures 5 to 8. Each device class uses a combination of the routes described in Annexes III, IV, V, VI and VII of the IVD MDD. For most common, low-risk 'other IVDs,' Annex III C Declaration of Conformity will be the route.

For self-test devices, the full quality system of Annex IV can be applied; alternatively, Annex III with design examination; or Annex V type examination with Annex VI product verification or Annex VII production quality audit.

For Annex II List B IVDs, the full quality system of Annex IV can be applied; or Annex V type examination with Annex VI product verification or Annex VII production quality audit.

For Annex II List A IVDs, the full quality system of Annex IV can be applied with design dossier examination; or Annex V type examination with Annex VII production quality audit.

Annexes IV and VII conformity assessment routes of the IVD MDD have surveillance requirements similar to the provisions of Annex IV, Section 5.

Annex VI has verification by examination and testing or sampling of every batch as part of its requirements, and under paragraph 3 states “The manufacturer must undertake to institute and keep up to date a systematic procedure to review experience gained from devices in the post-production phase and to implement appropriate means to apply any necessary corrective and notification action as referred to in Annex III, section 5.” This means post-market surveillance and systems to address issues raised are intrinsic to all the conformity assessment routes. Annex III, Section 5 makes this very clear; it starts by repeating the paragraph quoted above and goes on to state:

“…means to apply any necessary corrective actions, taking account of the nature and risks in relation to the product. He shall notify the competent authorities of the following incidents immediately on learning of them:

(i) any malfunction, failure or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to, or might have led to, the death of a patient or user or other persons or to a serious deterioration in his or their state of health;

(ii) any technical or medical reason connected with the characteristics or the performance of a device for the reasons referred to in subparagraph (i) leading to systematic recall of devices of the same type by the manufacturer.”

These conditions effectively cover both post-market surveillance and vigilance reporting.

5.2.1 Other IVDs

Annex III of the IVD MDD contains many requirements of a full quality system and should not be considered an easy option.

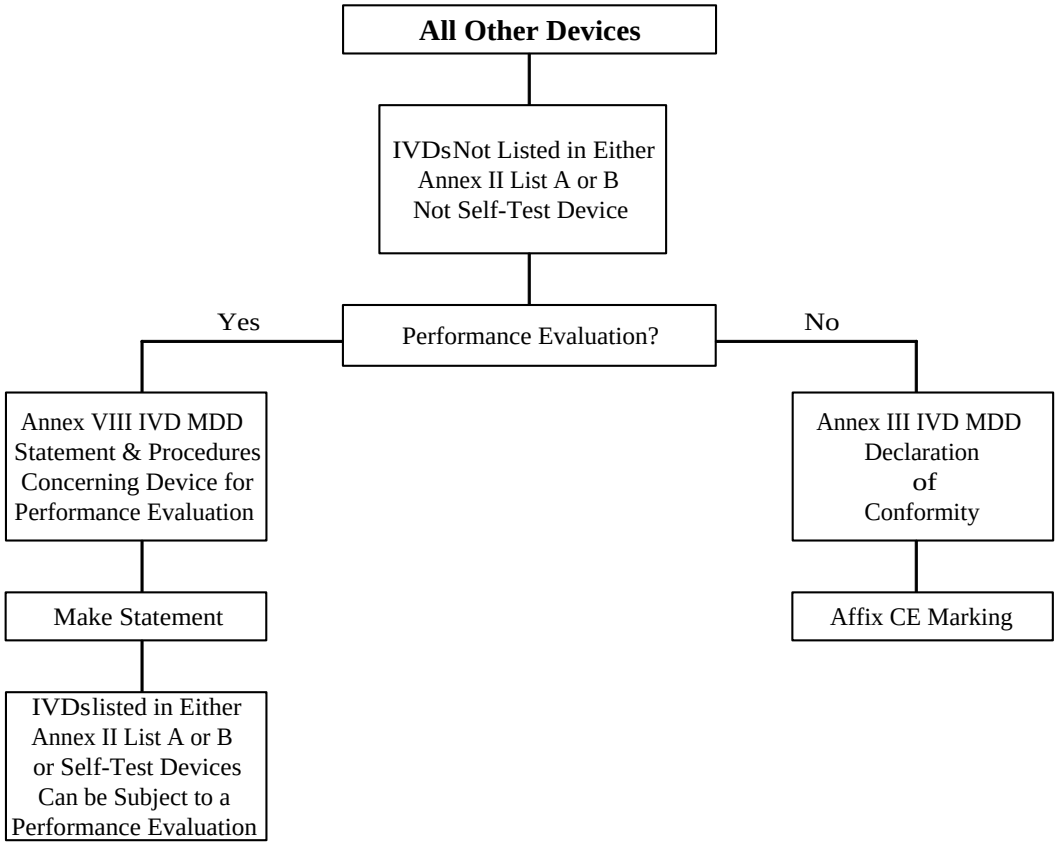

Figure 5: Other IVDs Conformity Assessment Procedures

5.2.2 Self-test IVDs

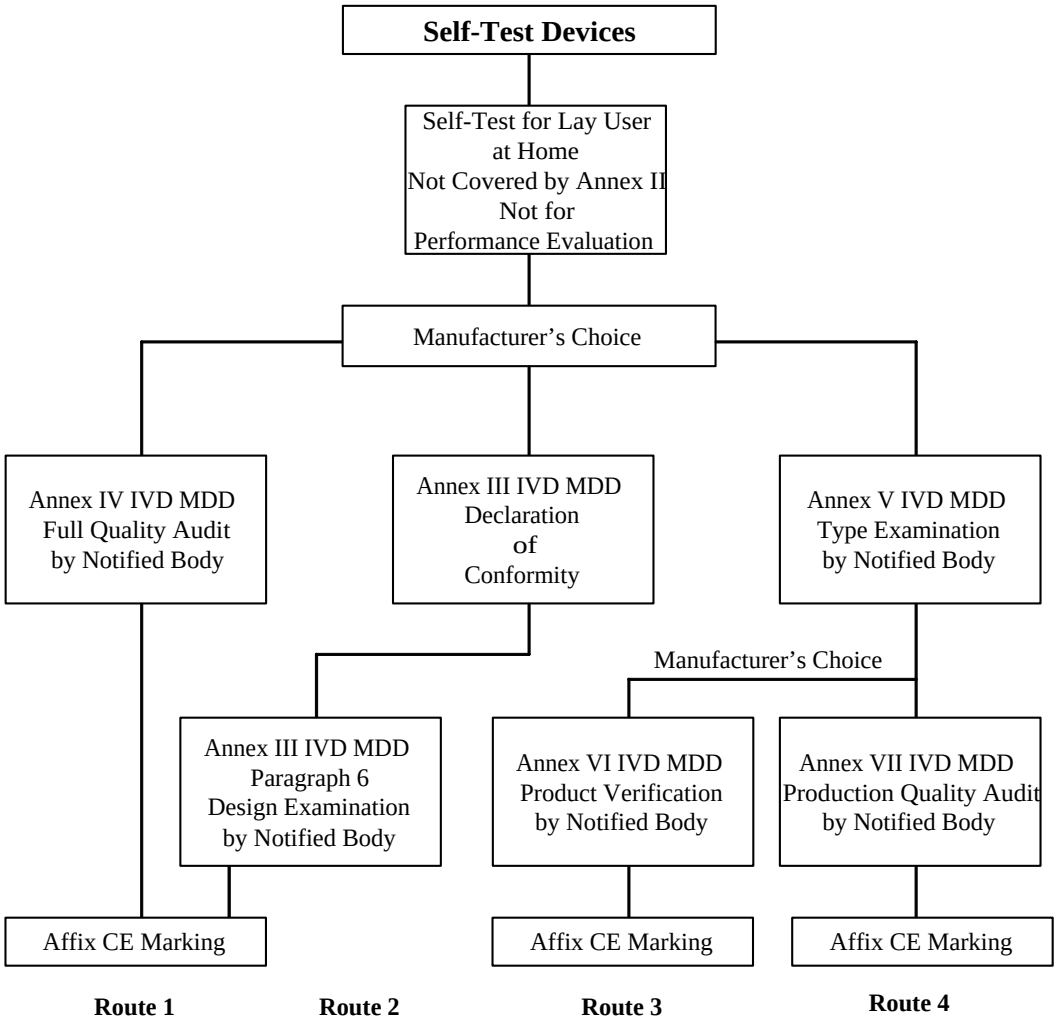

Figure 6: Self-Test IVDs Conformity Assessment Procedures

Route 1: Application of Annex IV

NB approves quality system to Annex IV of the IVD MDD, using EN ISO 13485: 2003.

Manufacturer makes written declaration of conformity and affixes CE marking.

Route 2: Application of Annex III

Manufacturer provides technical documentation to demonstrate the product's compliance with the IVD MDD. This includes a design examination by the NB.

Annex III of the IVD MDD contains many requirements of a full quality system and should not be considered an easy option.

Route 3: Application of Annex V with Annex VI

Manufacturer submits to NB a representative sample of product, or 'type,' along with supporting technical documentation, to assess compliance of type with the ERs of the IVD MDD. This may include tests to standards and characteristics specified by the manufacturer. When the NB has examined the type and verified that it was manufactured in conformity to technical documentation; and conducted tests to assess compliance of the type with the IVD MDD, an EC type examination certificate is issued.

NB examines/tests each individual product or sample to verify conformity to type approved in EC type examination certificate and the IVD MDD. Amount of testing will depend upon how much of the final testing by the manufacturer the NB approves.

NB affixes, or has affixed, its identification number to products approved and draws up certificate of conformity relating to the tests carried out.

Route 4: Application of Annex V with Annex VII

Manufacturer submits to NB a representative sample of product, or 'type,' along with supporting technical documentation, to assess compliance of type with the ERs of the IVD MDD. This may include tests to standards and characteristics specified by the manufacturer. When the NB has examined the type and verified that it was manufactured in conformity to technical documentation and conducted tests to assess compliance of the type with the IVD MDD, an EC type examination certificate is issued.

NB approves quality system to Annex VII of the IVD MDD, using EN ISO 13485: 2003, including any justified exemption from product realization as appropriate.

Manufacturer makes written declaration of conformity and affixes CE marking.

5.2.3 Annex II List B IVDs

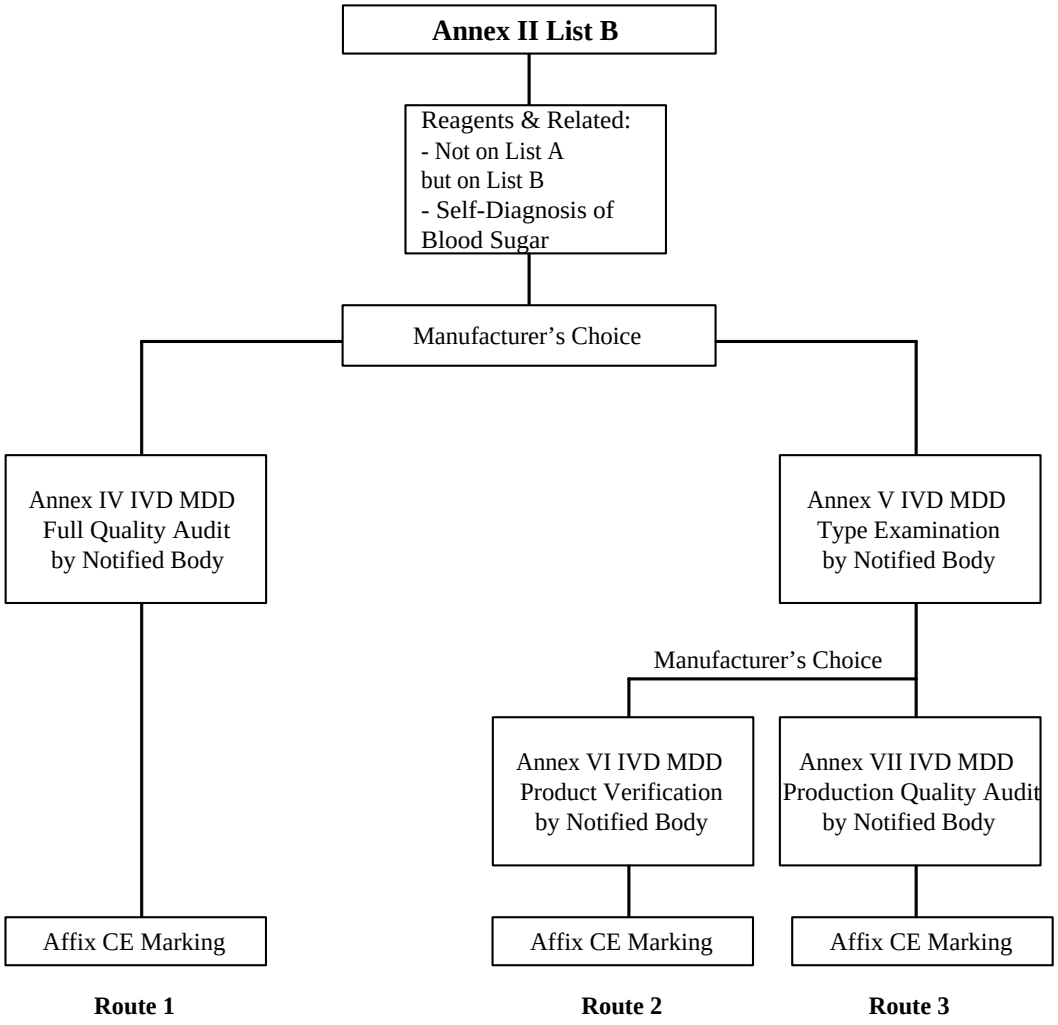

Figure 7: Annex II List BIVDsConformity Assessment Procedures

Route 1: Application of Annex IV

NB approves quality system to Annex IV of the IVD MDD, using EN ISO 13485: 2003.

Manufacturer makes written declaration of conformity and affixes CE marking.

Route 2: Application of Annex V with Annex VI

Manufacturer submits to NB a representative sample of product, or 'type,' along with supporting technical documentation, to assess compliance of type with the ERs of the

IVD MDD. This may include tests to standards and characteristics specified by the manufacturer. When the NB has examined the type and verified that it was manufactured in conformity to technical documentation and conducted tests to assess compliance of the type with the IVD MDD, an EC type examination certificate is issued.

NB examines/tests each individual product or sample to verify conformity to type approved in EC type examination certificate and the IVD MDD. Amount of testing will depend upon how much of the final testing by the manufacturer the NB approves.

Notified body affixes, or has affixed, its identification number to products approved and draws up certificate of conformity relating to the tests carried out.

Route 3: Application of Annex VI with Annex VII

Manufacturer submits to NB a representative sample of product, or 'type,' along with supporting technical documentation, to assess compliance of type with the ERs of the IVD MDD. This may include tests to standards and characteristics specified by the manufacturer. When the NB has examined the type and verified that it was manufactured in conformity to technical documentation and conducted tests to assess compliance of the type with the IVD MDD, an EC type examination certificate is issued.

NB approves quality system to Annex VII of the IVD MDD, using EN ISO 13485: 2003, including any justified exemption from product realization, as appropriate.

Manufacturer makes written declaration of conformity and affixes CE marking.

5.2.4 Annex II List A IVDs

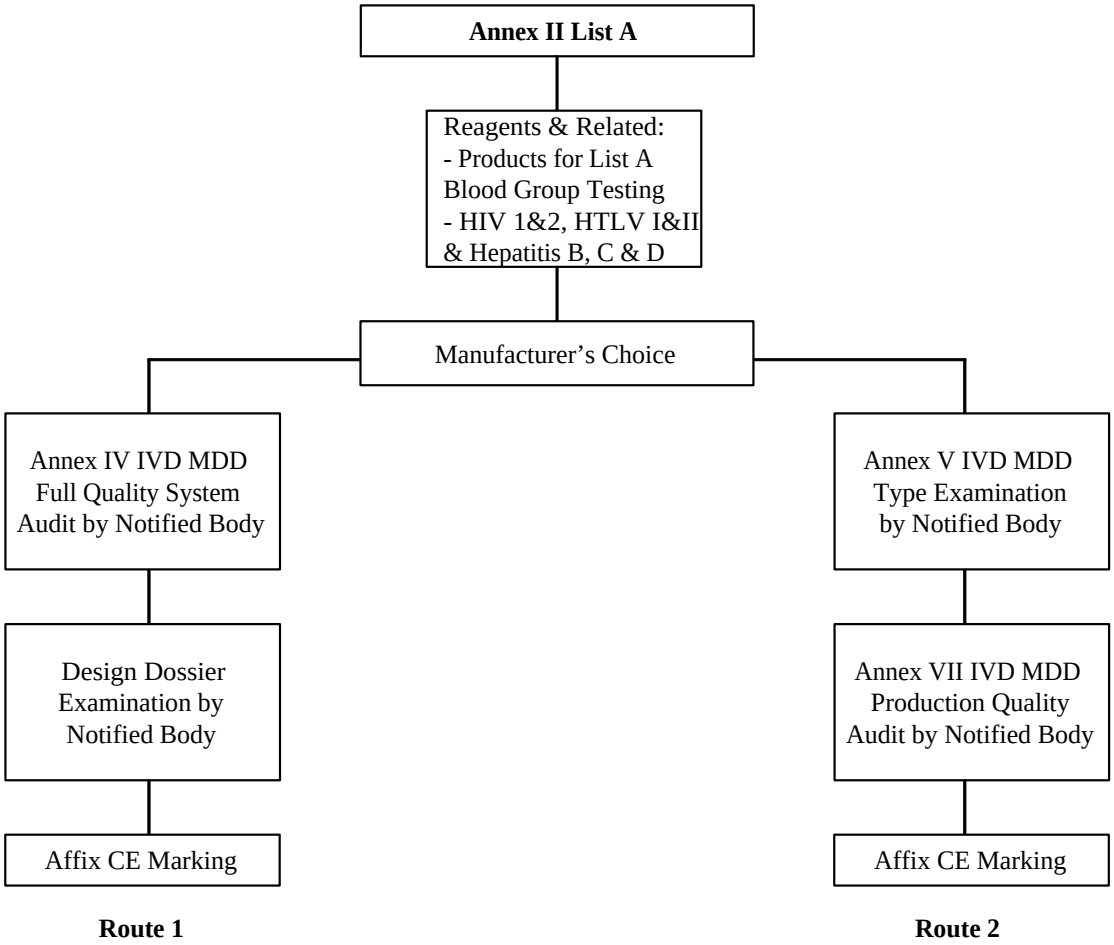

Figure 8: Annex II List A IVDsConformity Assessment Procedures

Route 1: Application of Annex IV + Design Dossier

NB approves quality system to Annex IV of the IVD MDD, using EN ISO 13485: 2003.

Manufacturer must provide a design dossier for examination by the NB before manufacture. If this is satisfactory, the NB will issue an EC design examination certificate, which will contain the "conclusions of the examination, conditions of validity, the data needed for the identification of the approved design and, where appropriate, a description of the intended purpose of the device." Changes to the design require approval from the NB in the form of a supplement to the EC design examination certificate.

The manufacturer must provide the NB with verification data carried out on the manufactured devices or each batch of devices. Samples of product need to be made

available to the NB in accordance with pre-agreed conditions and modalities.

Manufacturer makes written declaration of conformity and affixes CE marking. Note that Section 6.2 of Annex IV states “The manufacturer may place the devices on the market, unless the notified body communicates to the manufacturer within the agreed time-frame, but not later than 30 days after reception of the samples, any other decision, including in particular any condition of validity of delivered certificates.”

Route 2: Application of Annex V with Annex VII

Manufacturer submits to NB a representative sample of product, or ‘type,’ along with supporting technical documentation, to assess compliance of type with the ERs of the IVD MDD. This may include tests to standards and characteristics specified by the manufacturer. When the NB has examined the type and verified that it was manufactured in conformity to technical documentation and conducted tests to assess compliance of the type with the IVD MDD, an EC type examination certificate is issued.

NB approves quality system to Annex VII of the IVD MDD, using EN ISO 13485: 2003, including any justified exemption from product realization, as appropriate.

The manufacturer must provide the NB with verification data carried out on the manufactured devices or each batch of devices. Samples of product need to be made available to the NB in accordance with pre-agreed conditions and modalities.

Manufacturer makes written declaration of conformity and affixes CE marking. Note that Section 5.2 of Annex VII states “The manufacturer may place the devices on the market, unless the notified body communicates to the manufacturer within the agreed time-frame, but not later than 30 days after reception of the samples, any other decision, including in particular any condition of validity of delivered certificates.”

6 Other Features of the CE Marking Process

6.1 Post-market Surveillance and Vigilance Reporting

The MDD and IVD MDD require the manufacturer to review the experience gained in the post-production phase and to apply corrective actions where appropriate. Manufacturers are required to take a proactive approach to monitoring and assessing product performance in the marketplace, rather than waiting for an adverse incident to occur. Manufacturers shall establish and maintain a documented feedback system to provide an early warning of quality problems for input to their corrective action system. Such feedback could result from customer complaints, product returns, customer surveys or reports from competent authorities or other sources.

Article 2 of both the MDD and IVD MDD requires national competent authorities to take the necessary measures to ensure that products marketed within their jurisdiction do not compromise the safety and health of patients or users. Article 10 of the MDD and Article 11 of the IVD MDD require member states to investigate and act on any incidents brought to their attention. Where such incidents are brought to their attention by a medical practitioner or medical institution, the appropriate Competent Authority (CA) shall inform the manufacturer. Manufacturers have an obligation to inform competent authorities of incidents involving products marketed within that competent authority's jurisdiction. Such incidents are those that

led to a death;

led to a serious deterioration in the health of a patient, user or other person; or

might have led to a death or serious deterioration in health.

A manufacturer's vigilance reporting system includes the name and address of a person within the EU who is responsible for liaising with competent authorities. The reporting system also includes procedures for receiving incident reports, assessing those reports, communicating with concerned competent authorities, and issuing advisory notices and recalls. The important references for guidance are repeated here for completeness and ease of reference:
MEDDEV 2.12-1 rev 4 (April 2001) Guidelines on a Medical Devices Vigilance System is available from

http://europa.eu.int/comm/enterprise/medical_devices/meddev/2_12-1___04-2001.pdf

European CAs for the national vigilance systems are provided in the 'List of vigilance contact points within the National/Competent Authorities', which is available on the web at
http://europa.eu.int/comm/enterprise/medical_devices/ca/ca_vig.htm

This vigilance reporting system is somewhat similar to the US Medical Device Reporting (MDR) System. The European Commission produced Guidelines on a Medical Device Vigilance System

describe the types of incidents to be reported, indicate time frames for reporting, outline reporting format, and provide a listing of European competent authorities and their addresses.

6.2 European Authorized Representative

A manufacturer who places a product on the market in the manufacturer's own name must

have a registered place of business within the EU; or

designate someone, with a registered place of business within the EU, to be responsible for that product.

The manufacturer must provide the relevant CA with the name and address for the EU authorized representative as well as a description of the devices being placed on the market. Distributors can be designated as manufacturers' authorized representatives, but the commercial implications of such a position need to be carefully considered. The product label, the outer packaging or instructions for use shall contain the name and address of the designated authorized representative.

The designated authorized representative is the contact person for the competent authorities concerning incidents and related matters. Requests for technical files related to the product are directed to this person.

A designated authorized representative requires only a summary technical file, as described in Section 3.4.3 of this chapter. It is not necessary to make the full technical file available to a designated authorized representative. However, in the case of an incident investigation, a CA has the right to ask for any technical files. In these situations, a designated authorized representative is required to obtain such files from a manufacturer and hence, has access to the information contained in those files.

With respect to requests from NBs for technical files pertaining to device approval, the MDD does not require NBs to go through designated authorized representative(s) to obtain such files. In these situations, NBs and manufacturers can deal directly without having designated authorized representatives involved with the files.

6.3 Labeling

The MDD places strong emphasis on product labeling and instructions for use. The MDD and IVD MDD do not set out language requirements, but allow Member States to include language requirements when enacting Member State legislation to implement the directives. To date, all Member States have specified language requirements in their legislation. A manufacturer exporting to all Member States can expect to have to provide information in at least 20 languages and there are possibly another 6 languages to seriously consider with further expansion. This number of languages does not include provincial dialects or minority languages such as Welsh, Breton or Basque; nor does it include large indigenous ethnic groups that may need to be addressed for self test devices, such as Hindu or Urdu. A translation procedure is a necessity and expected.

Section 13 of Annex I (ERs) of the MDD specifies the type of information required and similarly Annex I (ERs), Section 8 of the IVD MDD. The language requirements for labeling can be partially addressed by using acceptable graphic symbols for product labeling as set out in the harmonized standard EN 980 *Graphical Symbols for Use in the Labeling of Medical Devices* and other harmonized standards for IVDs. Further information on language requirements can be obtained for the new Accession States by contacting the relevant CA in each Member State, or the Delegation of the European Commission in Canada, at the addresses listed under Information Sources, Section 7 of this chapter.

Given here is a brief summary of the best available current information on language requirements across Europe.

European Medical Device Labeling – Language Requirements

NB: National transpositions do vary and the use of the national language of each country is demanded. Some other variations do occur with clinical trials and other registration activities. The Czech Republic has demanded it inspects facilities but the EU is attempting to correct this as it goes against the Treaty of Rome principles that the EU is all about.

It is important to note that the CE marking is NOT a direct passport to pan-European trade as many people believe; there are always some differences such as language or detailed registration of certain higher risk products that differ from country-to-country.

Working on detailed requirements with country distributors or subsidiary companies and local native legal counsel is recommended.

The new Accession State countries follow the pre-existing Member States that have a long established transposition of the all the directives.

Austria

German is the transposition language of Austria. Exceptions can be possible but only in very special cases (e.g. for performance evaluation of IVDs).

Belgium

French ***and*** Dutch ***and*** German are the transposition languages used in Belgium and all must be used for patient instructions.

English is acceptable if one of the following conditions occurs:

- Medical specialists (users) are well educated in English language;
- Users (technical staff) have been trained by the manufacturer with courses/seminars; or
- The products are used routinely, i.e. require little in the way of instructions for use (IFUs).

Denmark

Unsurprisingly, Danish is the transposition language of Denmark, but "… the Agency can in exceptional cases allow the information to be in one or more of the other official language of the user".

Software screens need to be translated if it is necessary to use the instrument safely.

Finland

The transposition allows for instructions and language in Finnish, Swedish or English. However, there is a twist, in that for "safe use" the labeling needs to be in Finnish and Swedish.

France

Unsurprisingly, French is the transposition language of France.

Germany

Unsurprisingly, German is the transposition language of Germany. Another language easy to understand for the user may be used in reasoned cases, if information on safety is given in German or in the language of the user.

Greece

Instructions for use (IFU) need to be in Greek, but labels in one of the official EU languages are acceptable.

Instrument manuals are acceptable in English, but a short guide in Greek may be requested.

Iceland (EFTA)

Icelandic is required for labeling.

Ireland

English is the transposition language of Ireland.

Italy

Unsurprisingly, Italian is the transposition language of Italy, “at the moment of delivery to the final user”.

Liechtenstein

The transposition implies the use of Swiss requirements for language, i.e., German ***and*** French ***and*** Italian. This is a good approach for tiny Liechtenstein, i.e. use Swiss labeling.

Exceptions can be made if
1. The products are intended only for professional use;

2. It can be supposed that the professionals understand the English language and agree with it;

3. The protection of patients is guaranteed; and

4. The translation into German means a disproportionate amount work for the benefit.

Luxembourg

French or German or Luxembourgisch or English – for professional (doctors not nurses) use only, are acceptable languages in tiny Luxembourg. Again, Swiss type labeling is recommended.

Netherlands, The

Dutch is the transposition language in The Netherlands but English may be acceptable if: “that device is exclusively used in professional environment, under the condition that the user has an adequate mastering of English”. This needs to be checked with the CA/NB to be certain for each product.

Norway (EFTA)

Nordic languages or English acceptable: “Distributor / manufacturer shall, on informing user, take into consideration potential users’ education and competence”.

Portugal

Portuguese is the language of the transposition in Portugal [but English is acceptable on vial labels].

Spain

Unsurprisingly, Spanish is the transposition language of Spain.

[Surprisingly, Spain requires the labeling text to be submitted to the Competent Authority and a lot or serial number must be included for traceability for IVDs.]

Sweden

Swedish is the language of the transposition in Sweden. Exceptions from Swedish are in theory possible but only for truly exceptional cases that are well justified.

Switzerland

German ***and*** French ***and*** Italian are the transposition languages used in Switzerland. There has been talk in the past of Romansch (gipsy) being the fourth official language.

English acceptable as long as
- The manufacturer has the confirmation from the user that he can understand it;
- The user has the technical knowledge;
- The protection of patients, users and third parties is guaranteed;
- The safe and proper use of the device is not jeopardized;
- Providing the three languages is too burdensome (can you prove it?);
- Additional information in one of the official languages is provided upon request (this is also applicable for software screens).

United Kingdom

English is the language for all documentation.

New Accession States

The New Accession became full Member States of the EU on the 1st May 2004 and the most important states from a commercial perspective are Poland, Hungary and the Czech Republic. The others are Cyprus, Estonia, Latvia, Lithuania, Malta, Slovakia and Slovenia.

All these countries represent a total population of around 75 million people and a total market size for all medical devices of around US$1.5 billion. There are still some national requirements in addition to the medical directives for placing devices on the market and so these countries are relatively expensive to access when all the translation and documentation costs are totalled up.

Definitive answers on regulatory requirements are not possible for all countries as English source material is scarce and reliable secondary sources are necessary to bring what available information is known together here.

Poland

Poland's transposition of the directives is currently incomplete although it has allowed CE marked devices into its market since the 1st October 2002. The basic text has been transposed but amendments are required to align fully with the EU. A Draft Medical Device Act has been published. The basic texts are believed to be available in English.

The most recent information indicates that Poland has negotiated a transition period where medical devices, including IVDs, can be sold under the previous system until the 31st December 2005.

Currently manufacturers and suppliers of CE marked products need a local authorized representative and registration is necessary for both manufacturers and their products. This is not free movement of goods and all new Accession States may not prohibit, restrict or impede the placing on the market and putting into service products legally bearing the CE marking. The Polish requirement is expected to be changed and the change might already have been implemented by the time this guide is published.

New Approach Directives are supposed to supersede all corresponding national provisions and Member States must repeal all contradictory national legislation, hence the amendments. All labels and IFUs need to be in Polish. It is believed the use of English for professional use only devices is being considered as part of the Draft Medical Device Act Article 4.6. Poland does not yet have a CA listed on the Europa web site but does have some Notified Bodies.

The Polish CA can be contacted via Piotr Nerlewski at the
Department of Science and Medical Staff, Ministry of Health,
00-952 Warsaw, Miodowa 15 Str. Poland.
Tel: +48 22 634 8 553 /351; fax: +48 22 831 53 54; email: p.nerlewski@mz.gov.pl.
Further information sources: CA www.urpl.gov.pl / www.il.waw.pl and trade association www.polmed.org.pl

Hungary

Hungarian is the transposition language. Hungary does allow English on packaging labels but insists the IFU is in Hungarian and included with each device.

Bar coding of devices is believed to be mandatory.

Further information sources: http://amd.eum.hu/ and trade association: www.amdm.hu

Czech Republic

Requires Czech language, English is not accepted.

A reference for Czech law is www.sbirkyzakonu.cz and it could be useful to check with local counsel about the current status in more detail, as this is one of the larger recent Accession States.

Instructions for use may not be made available via CD-ROM or the Internet.

It is expected in the future that English versions of the Czech transposition will be available at the www.sukl.cz site.

The Czech Republic does require a notification before devices are placed on the market to be submitted to the Ministry of Healthcare. This includes a declaration of conformity in Czech after which companies must wait 30 days for the ministry to raise questions.
Further information sources: MoH CA www.mzcr.cz; SUKL www.sukl.cz/en04/en04.htm and trade association: www.czechmed.cz

Cyprus

English and Greek versions of the law and regulations will be available in the future on a newly constructed web site.

Cyprus does require some words for IVDs such as lot, sterile devices for performance evaluation to be written in Greek in all cases; however, the CA is considering an amendment allowing them in English for professional use. IFU in English is accepted for professional use. Software was not specified in the regulation.

Cyprus is in favour of electronic labeling and instructions.

Further information source: web site for CA under construction.

Estonia

This is the smallest country, with 1.4 million people, of the recent Accession States. Estonia has established laws in line with the MDD for several years.

All documentation must be in Estonian (similar to Finnish). However, given the small market size the Estonian government intends to take a pragmatic approach to language requirements considering both the availability and affordability of information for the potential user. The Estonian State Agency of Medicines has been reported as very positive about the use of e-labeling and this could be very helpful in such a small market.

Manufacturers, or their Authorized Representatives, are believed to have to issue a declaration of conformity to local legal requirements. A new law clarifying requirements should have now been passed but more research would be needed to be sure. A local authorized representative is not now mandatory. Further information source: CA www.sam.ee

Latvia

New regulations have been discussed during 2004 by the Cabinet of Ministers that will fully align with the EU. Clearly more regulations will follow and this situation requires monitoring. It is believed Latvia still requires a notification when devices are placed on the market that has to be submitted to the Health Statistics and Medical Technology Agency.

The European trade association Eucomed has reported that English and German labeling is likely to be acceptable for professional internal use only.

The Europa web site does not list the Latvian CA but further information may be available from www.vsmta.lv

Lithuania

Lithuanian language required. The Lithuania CA has stated electronic IFUs could be used and this could prove useful in the future if followed through into the regulations.

It is believed Lithuania accepts software in English.

Manufacturers or their authorized representatives in Lithuania must also notify the Lithuanian authorities that they are placing their devices on the market in Lithuania.

Further information source: CA www.sam.lt/vaspvt (English under construction).

Malta

Malta has completed the transposition of the medical devices directives, is available with further information at www.msa.org.mt , and also has a European form for registration that is in English.

Since Maltese and English are official languages of Malta, all documentation can be in English. Notification of placing devices on the market is required.

Malta will permit e-labeling and IFUs once they are accepted at the European level.

Slovakia

Slovakia has completed the transposition of the medical devices directives but little else is readily available. Slovak is the official language of Slovakia but it is believed some use of Czech in labeling is tolerated, but as this is an informal statement this needs further checking to be sure.

Slovakia requires a notification when devices are placed on the market to be submitted to the State Institute for Drug Control (SÚKL) but there is no requirement to wait for an agency response prior to marketing.

Slovakia did require the use of a local authorized representative and it is believed this is no longer the case (conference communication) after the 1st of May 2004. (If not, it would need to change under the free movement of goods that is fundamental to the EU.) The Europa web site does not list the Slovakian CA but contact can be made via
J. Zámocká email: pomocky-sukl@slovanet.sk
State Institute for Drug Control (SÚKL)
Karpaská ul. 23, Bratislava Slovakia.
Web: www.sukl.sk Tel: 02 524 533 39; fax: 02 524 533 43.
Further information source, trade association: www.skmed.sk

Slovenia

It is believed Slovenia allows IFUs for professional use products to be in either Slovenian or English. IFUs for self-testing products must be in Slovenian. Currently IFUs must be inside the packaging but Slovenia does appear more flexible and advanced than most new Accession States as the use of IFUs on CD-ROM and the Internet is being considered.

However, foreign manufacturers did have to have a legal representative in the country and all persons taking part in the trading of medical devices and IVDs must be registered on a list of authorized persons. This is not now mandatory after the 1st of May 2004 Accession.
Further information sources: CA http://www2.gov.si/mz/mz-splet.nsf
and trade association: www.gzs.si/DRNivo3.asp?ID=12412&IDpm=544

Further Enlargement

The next wave of EU enlargement is expected in 2007 for Bulgaria, Croatia and Romania.

Bulgaria

The language requirement can currently be satisfied with English, with the one exception of self-testing that requires labels and IFUs to be in Bulgarian.

It is understood that Bulgaria does require a copy of 'the manufacturing licence', proof of company registration in Bulgaria, labels and possibly samples. Approval can take several months. However, further research is required to be certain about these requirements.

Croatia

Croatia introduced its own medical device and IVD regulation in 2001 in response to deaths due to faulty dialysers and these are not aligned to the EU directives. However, they are now taking steps to align them.

Croatian is the mandated language on the packaging of products and IFUs that should accompany the product. English may sometimes be permitted on its own for professional use products.

It is believed IFUs may not be made available via CD-ROM or the Internet.

It is believed the regulatory submission requires manufacturers, or their legal representative, to obtain a report from the Institute of Immuno-biologicals before applying for registration at the health ministry and evidence must be provided of third party certification. Registration costs around US$500-600 and is valid for five years. Further research is required to be certain about these requirements.

Romania

Romania has transposed the main provisions of the medical directives.

Product labeling currently may be in English but Romanian is mandatory for IFUs and must accompany the product. Romania will consider electronic provision of IFUs in the future.

Romania says it accepts CE marking as an alternative to certification by a Romanian body but it is understood that Romania still demands manufacturers and suppliers to follow its national registration procedures. Further research required to be sure.

The manufacturer and authorized representative must be named in the registration and the authorized representative must be registered at the Health and Family Ministry; and both manufacturers and suppliers must register at the Health and Family Ministry too.

A Romania translation of the certificate issued by the NB needs to be supplied for the registration along with an original CE marking declaration of conformity plus a legally attested translation may well be required for higher risk devices. A copy of the user's manual, plus a Romania translation and technical specifications issued by the manufacturer are required in the submission plus a fee of around US$300 per product. Registration takes around a month but lasts for five years.

Turkey

Turkey is currently under discussion and Accession negotiation started at the end of 2004.

Language expected to be mandated is Turkish. IFUs need to be in at least two languages: Turkish and either French, German or English.

Others

Two other countries that are in Europe and will eventually enforce language requirements are Macedonia and Serbia.

7 Information Sources

There are a number of useful documents available to those pursuing the CE mark registration. These can be found in the *Official Journal of the European Communities* and in other European publications. Such documents include the various directives, lists of Notified Bodies, lists of harmonized standards, guidelines on the application of the various directives, and guidelines on vigilance reporting. A list of most useful and important documents is contained in Appendix 5 of the present guide.

The best Canadian source of information concerning the sale of medical devices in Europe is the Delegation of the European Commission in Canada. Information can be obtained by contacting their office or accessing their website. The Delegation's address is

Delegation of the European Commission
111 Albert Street, Suite 330
Ottawa, Ontario K1P 1A5

Tel: (613) 238-6464
Fax: (613) 238-5191
E-mail: admin@eudelcan.org

Some documents are available, free of charge, from their website (http://www.europa.eu.int) as indicated in various parts of this chapter.

Copies of relevant ISO and EN standards are also useful. Both ISO and EN standards can be obtained through the Global Information Centre at the address below:

Global Information Centre
240 Catherine Street
Ottawa, Ontario K2P 2G8
Tel. (613) 237 4250
Fax: (613) 237 4251
E-mail: gic@ihscanada.ca

The GIC also has a website (http://global.ihs.com).

Chapter 2: Canadian Requirements

An Overview of the Quality System Requirements for the Sale of Medical Devices in Canada

Health Canada, under the authority of the Food and Drugs Act, regulates the sale of medical devices and drugs in Canada. On July 1, 1998, new Medical Devices Regulations ("the Regulations") came into force, replacing Regulations that had been in effect since 1975. These regulations are amended from time to time to reflect new policies or minor housekeeping changes. A consolidated version can be viewed on the following website: http://laws.justice.gc.ca/en/f-27/sor-98-282/129451.html. The current Regulations are based on a risk assessment and risk management approach with a balance of pre-market review, quality systems and post-market surveillance.

One system classifies in vitro diagnostic devices. The second classifies all other medical devices and addresses the majority of devices available to Canadians. Both systems classify devices into one of four risk classes, Class I representing the lowest risk and Class IV the highest. The system for non-in vitro medical devices utilizes criteria such as invasiveness; length of invasiveness; body system exposed to the device; whether or not the device relies on a source of energy; whether the device diagnoses or is therapeutic; and whether or not the device delivers energy to the patient, in assigning a level of risk to a device. Special rules are included to classify, for example, devices incorporating animal tissues or devices that use recombinant DNA technology in their manufacture.

A set of safety and effectiveness requirements form the basis of the Regulations. These have been modeled on the "essential requirements" of the European Directives. For the majority of devices, demonstration of compliance with these requirements to Health Canada is assessed through a pre-market device licensing requirement; however, all devices are required to meet these safety and effectiveness requirements, as appropriate.

Before a Class II, III or IV medical device can be imported, sold or advertised for sale, a device licence must be obtained from Health Canada. Class I devices are exempt from device licensing requirements. Although manufacturers are responsible for classifying their devices, classification is subject to verification by Health Canada. The amount of information required to be submitted to obtain a device licence increases the higher the risk class of the device.

To monitor medical device distribution from the time of manufacture to use, importers and distributors are required to obtain an establishment licence. Manufacturers of Class I medical devices distributing directly to users are also required to obtain an establishment licence. Issuance of an establishment licence is contingent upon attestations from the applicant that recall, mandatory problem reporting and complaint handling procedures are in place, and that proper distribution records are maintained.

1 Key Elements of the Medical Devices Regulations

1.1 Scope of Application

The Regulations apply to

(a) The sale and advertising for sale of a medical device;
(b) The importation of a medical device for sale or for use on patients.

In vitro diagnostic products that are drugs or that contain drugs are also covered under these Regulations, as if they were medical devices.

1.2 Medical Device and In Vitro Diagnostic Device Classification

Medical devices are classified into one of four classes (I, II, III or IV), based on how the device is represented for use by the manufacturer. Class I devices represent the lowest risk and Class IV devices represent the highest risk.

Schedule I, Part I of the Regulations sets out the rules for classifying medical devices other than in vitro diagnostic devices (IVDDs). These rules cover various combinations of the following criteria:

- Whether or not the device is invasive (i.e., penetrating the body or in contact with intact skin);
- Duration that the device is invasive (e.g., less than or greater than 30 days);
- Method of achieving invasiveness (e.g., whether it is invasive through a body orifice or is surgically invasive);
- Anatomy affected by the device (e.g., central nervous system);
- Whether it is active or non-active (i.e., powered or non-powered);
- Special situations (e.g., devices utilizing animal tissue or contact lens solutions).

Schedule I, Part II sets out rules for classifying In Vitro Diagnostic Devices (IVDD). These rules are based on the degree of risk associated with the use of an IVDD. All IVDDs are classified into one of four classes. An IVDD with the highest risk is classified as Class IV while an IVDD with

the lowest risk is classified as Class I. Criteria used to determine the class of each IVDD include:

- Its indication(s) for use (the specific disorder, condition, or risk factor for which the test is intended);

- Its application (screening, patient-based testing/diagnosis, monitoring, etc.);

- The technical/scientific/medical expertise of the intended user (testing laboratories vs. near-patient testing);

- The importance of the information to the diagnosis (sole determinant or one of several determinants), taking into consideration the natural history of the disease or disorder including presenting signs and symptoms which may guide a physician; and

- The impact of the result (including both true and false positives and negatives, genetic testing, home testing) to the individual and/or the public health.

The intent of the four different classes within this classification can be described as follows:

Class IV IVDDs are those that, through their use, present a high public health risk to the community in general. These include IVDDs used for donor screening or for the diagnosis of life-threatening diseases caused by transmissible pathogens such as HIV and hepatitis viruses. These are diseases that result in death or long-term disability, that are often untreatable or require major therapeutic interventions and where an accurate diagnosis is vital to mitigate the public health impact of the condition.

Class III IVDDs are those that, through their use, present either a moderate public health risk or a high individual risk. They present a moderate public health risk, to the community in general or in some cases to a more confined environment such as a hospital, as they are used to detect transmissible agents that cause diseases. These diseases, although often treatable, may result in death or long-term disability if not treated in a timely manner and where an accurate diagnosis offers an opportunity to mitigate the public health impact of the condition. Examples include sexually transmitted agents and infectious agents that cause nosocomial infections. Class III IVDDs that present a high individual risk are those where an erroneous result would put the patient in an imminent life-threatening situation (e.g. IVDDs used in cases of suspected meningitis or septicaemia) or would have a major negative impact on outcome (e.g. result in death or severe disability) as they are a critical, or even the sole, determinant (cancer screening, prenatal screening). They may also present a high individual risk because of the stress and anxiety resulting from the information and the nature of the possible follow-up measures (e.g. genetic testing).

Class II IVDDs are those that, through their use, present either a low public health risk or a moderate individual risk. These present a low community risk because they detect infectious agents that are not easily propagated in a population or because they cause self-limiting diseases.

They present a moderate individual risk as they are not the sole determinant or, if they are, it is not likely that an erroneous result will cause death or severe disability, have a major negative impact on outcome or put the individual in immediate danger.

Class I IVDDs are those that, through their use, present a minimal risk such as general in vitro diagnostic laboratory equipment, microbiology and cell culture media and general diagnostic reagents.

Before classifying a device, a manufacturer must first determine if the product meets the definition of a "device" as it is defined in the Food and Drugs Act. If it is determined that the definition applies, the manufacturer must then determine whether or not the definition of "medical device" in the Regulations applies. It is important to note that the definition in the Regulations excludes devices for use on animals, and if this is the case for the product in question, the Regulations would not apply.

The classification process can be complex and is dependent upon the interpretation of each rule as applied to a given device. The manufacturer is responsible for conducting a self-assessment of the device to determine its class. Where a medical device can be classified into more than one class, the highest class applies. Guidance is available to assist manufacturers in classifying their devices. The "Keyword Index" was prepared by Health Canada prior to the implementation of the new Regulations. Although helpful, caution must be exercised in using this guidance as a number of inaccuracies can be found in the classification of devices within the document. The document contains a disclaimer to the effect that it is not the authoritative source, and that, if in doubt, manufacturers should contact Health Canada for a definitive classification. This guidance and guidance for the interpretation of the classification rules for medical devices can be found on the Health Canada website at

http://www.hc-sc.gc.ca/dhp-mps/md-im/applic-demande/guide-ld/index_e.html

Further guidance may be obtained by viewing the list of Canadian licensed medical devices on the following website: http://www.mdall.ca.
The classification rules for devices other than IVDDs are close to, but not identical with, the European classification rules. If one applied the classification rules for each jurisdiction to the same group of medical devices, there is a strong likelihood that all but a few would result in equivalent classifications.

The EU has four classes of medical devices that generally correspond to Canada's four classes, as illustrated in the following table.

Canadian Medical Devices Regulations		European Council Directive 93/42/EEC (MDD)
Class IV	generally corresponds to	Class III
Class III	generally corresponds to	Class IIb
Class II	generally corresponds to	Class IIa
Class I	generally corresponds to	Class I

Appendix 1 of this guide provides a sample listing of medical devices for each European device class. Using the above comparison table, one can see how these devices would be classified under the Canadian Classification Rules for Medical Devices. This list is based solely on the author's interpretation of the intended use of these devices and may not necessarily reflect Health Canada's determination of device class.

A manufacturer would be wise to confirm the class of a particular device with Health Canada before proceeding with the implementation of the quality system. This is particularly important when determining the quality system requirements for a particular device class.

1.3 General Requirements

The following general requirements apply to all medical devices, except those that are custom-made, imported or sold for special access, or used for investigational testing on human subjects. These general requirements are set out in Part I of the Regulations. Requirements for devices that are custom-made or imported or sold for special access are set out in Part II. Requirements for devices used for investigational testing on human subjects are set out in Part III.

1.3.1 Safety and Effectiveness Requirements

Manufacturers must ensure that the medical device meets specific safety and effectiveness requirements as set out in Sections 10 to 20 of the Regulations. These requirements apply to all medical devices, except those that are custom-made; imported or sold for special access; or used for investigational testing on human subjects. The manufacturer must maintain records to demonstrate that these requirements are being met.

The safety and effectiveness requirements call for measures to ensure that the health or safety of patients, users or others is not adversely affected. They deal with

- The design and manufacture of the device;
- The degree of acceptable risks weighed against the benefits;
- The performance of the device;

- Protection against deterioration of the device's characteristics and performance;
- Protection of the device's characteristics and performance during transportation and storage;
- Compatibility of materials used in the device's manufacture;
- Minimizing the risk from reasonably foreseeable hazards (flammability, explosions, contamination, chemicals, microbial residue, radiation, electrical, mechanical or thermal hazards, and fluid leakages);
- Appropriately controlled sterilization processes;
- Compatibility with all other parts of the system with which it interacts;
- Accurate and consistent measuring capability, where a measuring function is involved;
- Validation of software, where software is involved;
- Labeling.

These safety and effectiveness requirements closely correspond to the essential requirements of the European MDD (ref: Annex I of the MDD). However, the MDD spells out the essential requirements in much greater detail. Similar to the European approach and the references in the MDD to the use of harmonized standards for complying with the essential requirements, Health Canada has developed a policy on the use of recognized standards in establishing the safety and effectiveness of medical devices. This policy can be found on the Health Canada website at the following address:

http://www.hc-sc.gc.ca/dhp-mps/md-im/applic-demande/guide-ld/index_e.html

1.3.2 Medical Device Licence

Manufacturers must hold a licence for Class II, III and IV medical devices imported, sold or advertised for sale in Canada. Applications for a device licence must be submitted to Health Canada and must contain detailed information as set out in the Medical Device Licence section of the Regulations. This information must include specific quality system requirements as identified in that section. These requirements are described in Section 2 of this chapter.

Health Canada, upon satisfying itself that the device meets the safety and effectiveness requirements described above, will issue a device licence, which is subject to annual renewal. This annual renewal will require manufacturers to verify device information on file with Health Canada. Failure to renew a device licence will result in its cancellation by Health Canada.

1.3.3 Establishment Licence

Any person who imports or sells a medical device in Canada, and any manufacturer of a Class I device that does not import or distribute solely through a person who holds an establishment licence, must hold an establishment licence. Retailers, health care facilities, and manufacturers of Class II, III and IV devices are exempt from this requirement. Applications for an establishment licence must be submitted to Health Canada and must contain detailed information as set out in the Establishment Licence section of the Regulations. Health Canada, upon satisfying itself that the establishment meets the requirements described in that section, will issue an establishment licence, which is valid for one year. Health Canada can refuse to issue or can cancel an establishment licence. Further guidance on Establishment Licensing can be found on the Health Canada website at

http://www.hc-sc.gc.ca/dhp-mps/md-im/applic-demande/guide-ld/index_e.html

1.3.4 Labeling Requirements

Medical devices imported or sold in Canada must have labels containing specific information, related to these devices, that is easily understood by the user. Where the device is too small to permit this information to be placed on the label, the information must be contained in the directions for use.

Licences and licence applications must contain a street address. A postal code can be included as additional information, but not as a replacement for a street address. These requirements are set out in the Labeling Requirements section of the Regulations. This section also sets out language requirements related to labels and directions for use. It is important to note that the address on the device licence must match the address on the quality system certificate. For example, you cannot have a street address on the licence and only a postal code on the quality system certificate. Both require a street address, although it is permissible for one to have a postal code in addition to the street address, and the other not to include a postal code. Further guidance on Labeling Requirements can be found on the Health Canada website at

http://www.hc-sc.gc.ca/dhp-mps/md-im/applic-demande/guide-ld/index_e.html

1.3.5 Distribution Records

A manufacturer, importer or distributor of a medical device must maintain distribution records of each device. This requirement does not apply to retailers or health care facilities in respect of devices used within that facility. The Distribution Records section of the Regulations sets out the information to be contained in these records, as well as additional requirements for implants.

Records must be retained for the projected life of the device, as defined by the manufacturer, but not less than two years after the device was dispatched from the manufacturer. Record retention times are the same as those for the EU and US.

1.3.6 Mandatory Problem Reporting

The manufacturers and the importers of devices must make preliminary and final reports to Health Canada concerning any incident involving their device that

(a) Is related to the failure or deterioration of the device or inadequacies in the labeling or directions for use; and
(b) Has led to a death or serious deterioration in the health of a patient, user or other person; or could have led to a death or serious deterioration in the health of a patient, user or other person.

The Mandatory Problem Reporting section of the Regulations sets out the types of incidents to be reported, time frames for reporting and content for the preliminary and final reports including actions taken to prevent the incident from recurring.

These mandatory reporting requirements are harmonized with the European vigilance reporting requirements described in Section 6.1 of Chapter 1 of this guide.

Further guidance on the Mandatory Problem Reporting requirements of the Regulations can be found on the Health Canada website at

http://www.hc-sc.gc.ca/dhp-mps/md-im/applic-demande/guide-ld/index_e.html

1.3.7 Recall

A manufacturer, importer or distributor of a medical device must make provisions for carrying out the following:

- An effective and timely investigation of reported problems relating to the performance or safety of the device, including any customer complaints;
- An effective and timely recall of the device.

Before undertaking the recall of a device, both the manufacturer and the importer must provide Health Canada with the detailed information set out in the Recall section of the Regulations. After such a recall, the manufacturer and the importer must report to Health Canada the results of the recall and the action taken to prevent a recurrence of the problem. The manufacturer and the importer must maintain records related to the recall. Further guidance on the recall requirements of the Regulations can be found on the Health Canada website at

http://www.hc-sc.gc.ca/dhp-mps/md-im/applic-demande/guide-ld/index_e.html

1.3.8 Implant Registration

The Implant Registration section of the Regulations sets out specific requirements of the manufacturer pertaining to the registration of implants and the use of implant registration cards to facilitate the provision of advisory information to patients. Devices subject to these requirements are listed in Schedule II of the Canadian Medical Devices Regulations. Health Canada may authorize methods of implant registration other than implant cards.

1.4 Custom-Made Devices and Medical Devices to be Imported or Sold for Special Access

To import or sell Class III or IV custom-made devices or devices for special access, particular requirements must be met in relation to authorization, additional information, labeling, distribution records, reporting of incidents, and advertising. These requirements are covered in Part II of the Regulations. Special access is defined in the Regulations as "access to a medical device for emergency use or if conventional therapies have failed, are unavailable or are unsuitable." Guidance on how to apply for authorization to obtain custom-made or special access devices can be found on the Health Canada website at

http://www.hc-sc.gc.ca/dhp-mps/md-im/applic-demande/guide-ld/index_e.html

Quality system requirements, identified in the Medical Device Licence section, Part I of the Regulations, do not apply to these categories of medical devices.

1.5 Medical Devices for Investigational Testing

A manufacturer or importer of a Class II, III or IV medical device may sell a device to a qualified investigator for the purpose of conducting investigational testing involving human beings if authorized by Health Canada and if the required records and documents are kept. For Class I devices, such authorization is not required if the required records and documents are kept. For all classes of these devices, particular requirements are set out in relation to record keeping, authorization, additional information, labeling, advertising, and other matters. These requirements are covered in Part III of the Regulations. Guidance on how to apply for authorization to conduct investigational testing on human subjects can be found on the Health Canada website at

http://www.hc-sc.gc.ca/dhp-mps/md-im/applic-demande/guide-ld/index_e.html

Quality system requirements, identified in the Medical Device Licence section, Part I of the Regulations, do not apply to this category of medical device.

1.6 Export Certificates

The exporter of a medical device must maintain, at their principal place of business in Canada, records that contain the completed export certificates and must submit these certificates to Health Canada inspectors for examination when asked to do so. Export certificates must be retained for not less than five years after the date of export.

Part IV of the Regulations sets out the requirements pertaining to export certificates.

2 Quality System Requirements

The quality system and related requirements are set out in Sections 32(2), 32(3), 32(4), 32.1, 32.2, 32.3, 32.4, 32.5, and 43.1 of the Regulations.

Manufacturers of Class II, III and IV devices must demonstrate that their devices are manufactured in accordance with internationally recognized quality system standards for medical devices. Presently the Canadian adoption of ISO 13485:1996 and ISO 13488:1996 are required by the Regulations. As of March 15, 2006, the international standard for medical devices will be ISO 13485:2003 *Medical devices—Quality management systems – System requirements for regulatory purposes*. ISO 13485:2003 embodies all the principles of Good Manufacturing Practices (GMP) widely used in the manufacture of medical devices. It is a stand-alone standard, with the same format and much of the same requirements as ISO 9001:2000 *Quality management system—Requirements*.

Canada has adopted ISO 13485:2003 as a Canadian National Standard and labeled it CAN/CSA-ISO 13485:2003. For class II devices, the quality system must satisfy the requirements of CAN/CSA-ISO 13485:2003, excluding design. For class III and IV devices, the quality system must satisfy the requirements for CAN/CSA-ISO 13485:2003, including design. Manufacturers operating under CAN/CSA-ISO 13485-98 and CAN/CSA-ISO 13488-98 quality systems have until March 15, 2006 to switch over to the 2003 version.

It is recommended that the scope of the organization’s quality system, as defined in its quality manual, address all appropriate sections of Part 1 *Canadian Medical Devices Regulations*.

During the third-party audit, the organizations must demonstrate how it has effectively implemented the above.

Demonstration of conformance with the quality system requirements will be required at the time an application is made for a medical device licence. Manufacturers will need to provide a copy of a quality system certificate, which has been issued to them by any third-party audit organizations (registrars) accredited by the Standards Council of Canada (SCC) and recognized by them and Health Canada under the Canadian Medical Devices Conformity Assessment System (CMDCAS) scope. For annual licence renewals, copies of the quality system certificate will not be required to accompany the renewal application. However, where a quality system certificate has been revised or amended as a result of a third-party audit by a registrar, the manufacturer must submit a copy of the revised or amended certificate to Health Canada within 30 days of the date of issue.

To view the most current list of accredited registrars, visit the Health Canada website at http://www.hc-sc.gc.ca/dhp-mps/md-im/applic-demande/guide-ld/index_e.html

2.1 Policy on the Canadian Medical Devices Conformity Assessment System (CMDCAS)

CMDCAS outlines Health Canada's policy on the processes leading to SCC's accreditation of registrars, and the registration of a medical device manufacturer's quality system by these accredited registrars. A Health Canada-SCC Management Committee is responsible for managing CMDCAS accreditation-related issues.

Health Canada will have full access to information related to an accreditation assessment, reassessment or surveillance audit of a registrar, and from a registrar's assessment, reassessment or surveillance audit of a manufacturer, and will treat this information in accordance with appropriate federal regulations and guidelines dealing with confidential or proprietary information.

The resolution of complaints and disputes surrounding a manufacturer's compliance with the regulatory requirements is the responsibility of Health Canada and will be resolved through a formal appeal process.

2.2 Registering the Quality System

2.2.1 The Process

To prove conformity with an ISO standard, organizations normally contract the services of registrars. Registrars conduct independent third-party audits of a company's quality system. If the company passes the audit, the registrar recommends that the quality system be registered to

the appropriate ISO standard.

Registration is normally valid for three years. There are three audits associated with the registration process:

1) The documentation audit, during which auditors assess the organization's quality system documentation, including the organization's policies and procedures, against the ISO standard;

2) The initial on-site audit, during which auditors assess the company's quality system against the ISO standard. They verify records, question selected staff members about work practices that affect product or service quality, and ensure that the organization's stated quality practices are indeed being followed. If the audit is successful, the registrar will recommend ISO registration; and

3) Surveillance audits, which are conducted once or twice per year to assess segments of the company's quality system to ensure continued compliance with the ISO standard. All segments of a company's quality system are typically audited over a three-year period. After the third year of registration, a comprehensive on-site audit is normally conducted and the surveillance audit process is repeated.

A registrar's audit may result in one of three situations:

1) The quality system conforms and the registrar will recommend ISO registration;

2) A major nonconformance is found and a recommendation for registration cannot be made. A major nonconformance means the absence, or total breakdown, of one of the ISO elements or a number of nonconformities throughout various elements, which the registrar considers would result in a breakdown of the quality system. A major nonconformance would also include the absence of any applicable section of Part 1 of the *Canadian Medical Devices Regulations,* which should be included in the scope of the quality system. While registrars do not audit against the *Canadian Medical Devices Regulations,* they are required to raise nonconformities against the relevant clause of ISO 13485. A number of clauses in ISO 13485:2003 stipulate that additional requirements must be meet where national or regional regulations call for these. For example, an auditor may find that mandatory problem reporting does not satisfy the *Canadian Medical Devices Regulations,* and will issue a nonconformance clause 8.5.1 of ISO 13485:2003. That clause requires documented procedures to notify the regulatory authorities of adverse incidents that meet their reporting criteria. It is Health Canada's responsibility to inspect for compliance against specific sections of the regulations. Where a major nonconformity is found, the organization being audited would be told to submit a revised plan to seek registration. On the basis of that plan, a re-audit would be scheduled; or

3) A minor nonconformity or observation, where a weakness in the quality system is discovered by auditors that is not severe enough to lead to a complete quality system breakdown but should be addressed. Often, auditors will recommend registration on the condition that the minor nonconformity or observation be rectified before the first surveillance audit.

In Canada, registrars are accredited by the Standards Council of Canada. To become accredited, registrars must comply with strict Standards Council of Canada requirements.

2.2.2 Registration Cost

Estimating the cost of registration is difficult, as it is influenced by such factors as the size of the organization being audited, and the number and complexity of its products. However, the costs will likely be similar to those identified in Section 3.3.3 of Chapter 1 relating to the CE mark. It is reasonable to assume that a manufacturer in the size range of 30 employees, manufacturing a Class II, III or IV device would have to pay between $25,000 and $30,000 for a quality system registration. This estimate includes travel and related costs, as well as semi-annual or annual surveillance audits.

3 Information Sources

General information on the Medical Devices Regulations can be obtained from Health Canada by contacting

Medical Devices Bureau
Room 1605, Main Statistics Canada Building
Postal Locator 0301H1
Tunney's Pasture
Ottawa ON
K1A 0L2

Tel.: (613) 957-4786
Fax: (613) 957-7318
Email: don_boyer@hc-sc.gc.ca
nancy_shadeed@hc-sc.gc.ca

An electronic version of the Regulations can be obtained from Health Canada's Website:
http://www.hc-sc.gc.ca/dhp-mps/md-im/applic-demande/guide-ld/index_e.html

Chapter 3: US Requirements

An Overview of the Quality System Requirements for Medical Devices Manufactured, Imported or Offered for Import in the US

Introduction

The US Food and Drug Administration (FDA), under the authority of the Federal Food, Drug & Cosmetic (FFD&C) Act, commenced the modern era of regulation of medical devices with the Medical Device Amendments of 1976 (the amendments). This has been modified significantly in more recent years by the Safe Medical Devices Act (SMDA) of 1990; the Medical Device Amendments of 1992; the Modernization of Act of 1997, known as 'FDAMA' and Medical Device User Fee and Modernization Act (MDUFMA) of 2002. These various acts regulate the medical devices manufactured, imported or offered for import in any State or Territory of the US, the District of Columbia or Puerto Rico. FDA regulation applies to manufacturers of finished devices intended for human use, and not to manufacturers of components or parts of finished devices. Quality system requirements are set out in the FDA's Quality System Regulation, Part 820 of 21 CFR (Code of Federal Regulations). These are described in Section 2 of this chapter and need to be read in detail and monitored for changes, especially new guidance notes that are both useful and expected to be followed by FDA.

Medical devices regulation is controlled by the Center for Devices and Radiological Health (CDRH), an excellent source of information that must be used by manufacturers to ensure regulatory compliance is achieved. The web site is found at: www.fda.gov/cdrh and there is an A-Z Index available. **Device Advice is considered to be essential reading for all those involved in US regulatory compliance, please see www.fda.gov/cdrh/devadvice/**. This guide is written as a complement to Device Advice that provides regularly updated critical and definitive information for all medical device manufacturers wishing to place medical devices on the US market and it is hard to overstate its importance in these matters. Key topics covered at Device Advice include:

- Overview of Regulations;
- Classify Your Device;
- How to Market Your Device;
- Registering Your Establishment;
- Listing Your Device;
- Pre-market Notification 510(k);
- Investigational Device Exemption;
- Pre-market Approval;
- Quality Systems;
- Medical Device Labeling;
- Medical Device Reporting;
- Medical Device Recall;
- Importing Devices;
- Medical Device Tracking;

- Post-market Surveillance;
- Guidance Documents;
- CDRH Databases;
- Code of Federal Regulations;
- Regulatory Manuals;
- International Information; and
- Consumer Information.

There is also a search function available and is worth using when trying to find the more obscure or older references to certain medical devices that may not be listed in Device Advice or the A-Z Index. On the CDRH home page there is a section 'Information Resources' that includes links to 'Contacts in CDRH' that can help you find an appropriate person at FDA for your enquiry.

Some devices containing biological tissue or used in conjunction with a drug may require reference to either the Center for Biologics Evaluation and Research (CBER) www.fda.gov/cber or the Center for Drug Evaluation and Research (CDER) www.fda.gov/cder, respectively.

1 Key Elements of the FDA Regulations

1.1 Device Classification

The level of FDA regulation is governed by the class of the device. Devices fall into three classes, I, II or III, with Class I devices, the lowest risk, requiring the least stringent controls and the highest risk Class III devices requiring the most stringent controls.

The process for arriving at an FDA device classification is significantly different from the process for classifying devices under Canada's Regulations and under the various European directives. The latter jurisdictions use device classification rules.

The FDA seeks advice and recommendations from panels of experts on device classification. On the basis of these recommendations, the FDA determines which class is appropriate, in terms of assuring the safety and effectiveness of each device, and classifies or reclassifies the device by regulation. The proposed classification regulation is then published in the Federal Register for public comment before a final order is issued. The FDA publishes a final regulation classifying medical devices. All medical devices marketed prior to May 28, 1976 have been classified and these are referred to as preamendment devices. Manufacturers can obtain information about a device's classification by contacting the FDA (see Information Sources, Section 3 of this chapter).

To get a definitive determination of the classification of a medical device by FDA requires the submission of product description, including the intended use, to FDA under the so-called "513(g)" procedure:

"For products regulated by CDRH, requests for classification information under section 513(g) of the act should be submitted to the attention of the 513(g) Coordinator, Food and Drug Administration, Center for Devices and Radiological Health, 510(k) Document Mail Center (HFZ-401), 9200 Corporate Boulevard, Rockville, MD 20850."

Sec. 513(g) of the Federal Food, Drug, and Cosmetic Act (p.132) states:

"(g) Within sixty days of the receipt of a written request of any person for information respecting the class in which a device has been classified or the requirements applicable to a device under this Act, the Secretary shall provide such a person a written statement of the classification (if any) of such device and the requirements of this Act applicable to the device."

It is vital to be clear about the classification at the earliest stage of product development since the introduction of User Fees with MDUFMA means that the costs (see later section for details), just for applying for different types of pre-market review vary enormously.

As a first step, a manufacturer placing any class of device on the market should determine whether there is a substantially equivalent legally marketed device, which has already been classified. Nearly all Class I devices are pre-market notification exempt and so are some Class II devices. If a pre-market notification is required and a substantially equivalent legally marketed device (known as a predicate device) is found, a Pre-market Notification for Class II devices (and a few Class I devices), commonly referred to as a 510(k), can be submitted to the FDA (ref: Section 1.2.3 of this chapter). If the FDA finds the device to be substantially equivalent (SE) to the predicate device, it will review the 510(k), and the device class will automatically fit into the same class as the predicate device. During the review, FDA may find the device is not substantially equivalent (NSE) or is truly novel and make a so-called De Novo ruling. Please see

www.fda.gov/cdrh/modact/classiii.html where a full explanation is provided:

"The legislative history of this provision contemplates a process that permits the Secretary (FDA, by delegation) to reclassify certain low risk devices into class I or II on the basis of established risk-based classification criteria when a new device is classified into class III under the statute because there is no predicate device to which it can be found substantially equivalent."

If the device is ruled Class III because there are no substantially equivalent predicate devices to a legally marketed device, manufacturers must submit a Pre-market Approval (PMA) Application to the FDA to enable the FDA to assess the device class (see Pre-market Approval, Section 1.4 of this chapter). This is a complex and expensive process.

Devices classified by the FDA do not always correspond to the equivalent Canadian or EU device class. However, in the majority of cases they will correspond. The following table illustrates the general relationship among the device classes of the three jurisdictions.

US FDA Device Classifications	Canadian Medical Devices Regulations	European Council Directive 93/42/EEC (MDD)
Class III	Class IV	Class III
Class III	Class III	Class IIb
Class II	Class II	Class IIa
Class I	Class I	Class I

FDA applies increasing levels of controls for increasing risk of devices:

Class I devices are subject to General Controls, which include establishment (manufacturing site) registration; device listing; Pre-market Notification (510(k)); records and reports; and Good Manufacturing Practices (GMP). However, note that nearly all Class I devices are exempt from 510(k) requirements and many from GMP. These devices are listed in the final classification regulation for the specific device. It is also important to note that all devices, including Class I utilizing software are subject to design controls.

Class II devices are subject to Special Controls, in addition to General Controls. These Special Controls may include additional requirements related to post-market surveillance, labeling, patient registries, guidelines and mandatory performance standards. For life-sustaining and life-supporting Class II devices, the FDA must identify the Special Controls necessary to provide adequate assurance of safety and effectiveness and describe how such controls provide the required assurances.

Class III devices are subject to Special Controls, in addition to General Controls but require the completion of a PMA [or rarely 510(k)] before a device can be marketed. Device Advice (www.fda.gov/cdrh/devadvice/pma/) provides a useful summary:

“Pre-market approval (PMA) is the FDA process of scientific and regulatory review to evaluate the safety and effectiveness of Class III medical devices. Class III devices are those that support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury. Due to the level of risk associated with Class III devices, FDA has determined that general and special controls alone are insufficient to assure the safety and effectiveness of Class III devices. Therefore, these devices require a pre-market approval (PMA) application under section 515 of the FD&C Act in order to obtain marketing clearance. Please note that some Class III preamendment devices may require a Class III 510(k).”

“PMA is the most stringent type of device marketing application required by FDA. The applicant must receive FDA approval of its PMA application prior to marketing the device. PMA approval

is based on a determination by FDA that the PMA contains sufficient valid scientific evidence to assure that the device is safe and effective for its intended use(s). An approved PMA is, in effect, a private licence granting the applicant (or owner) permission to market the device. The PMA owner, however, can authorize use of its data by another."

A measure of the difference between a 510(k) and PMA is reflected in the FDAMA change allowing manufacturers to promote a device with a successfully completed PMA or IDE as "FDA Approved" and that a successful 510(k) only allows a device to be marketed in the US and is thus only "cleared for marketing". No direct reference to the 510(k) that implies in any way endorsement or approval by FDA is allowed by manufacturers – even if FDA does this them selves! For more please see www.fda.gov/cdrh/devadvice/3315.html#promo and http://www.fda.gov/cdrh/devadvice/371.html#labeling

If the FDA determines the device is not substantially equivalent to a legally marketed device, the manufacturer must obtain a PMA or have the device reclassified into Class I or Class II before marketing the device.

1.2 General Controls

All devices are subject to General Controls. These require a manufacturer to

- Register each manufacturing establishment;
- List marketed medical devices;
- Submit a 510(k) before marketing a device that is new to the manufacturer or has been significantly modified; and
- Manufacture devices in accordance with the GMP regulation.

1.2.1 Establishment Registration

An owner or operator of an establishment, including foreign establishments (see FDAMA Section 417 and www.fda.gov/cdrh/devadvice/341.html) must register with the FDA within 30 days of commencing manufacturing operations on a device intended for human use. In certain instances, an owner or operator may be exempt under Section 510(g) of the Federal Food, Drug and Cosmetic (FFD&C) Act. Activities requiring registration include the repackaging, labeling and distribution of imported or domestic devices; and specifications development. Distributors were required, under the Safe Medical Devices Act (SMDA), to register with the FDA but since 1995, the FDA has exercised its enforcement discretion and is not currently requiring or accepting registration or listing forms from domestic distributors. Under FDAMA Section 23, wholesale distributors of devices are no longer required to register their establishment with the FDA, provided they do not do anything to make them a manufacturer. 'Guidance for Industry Instructions for Completion of Medical Device Registration and Listing Forms FDA 2891, 2891a and 2892' is available from the FDA website.

The **United States Agent for Foreign Establishments** became effective February 11, 2002, (please see www.fda.gov/cdrh/devadvice/341.html#USA) so "all foreign establishments must notify FDA of the name, address and phone number of their United States agent. Even if an establishment manufactures various medical devices, drugs, and/or biological products, each establishment site can designate only one United States agent. The United States agent must either reside in the U.S. or maintain a place of business in the U.S. The United States agent cannot use a post office box as an address. The United States agent cannot use an answering service. The agent must be available to answer the phone or have an employee available to answer the phone during normal business hours. The Official Correspondent for registration may also be the United States agent for the establishment, but this is not required.

The responsibilities of the United States agent are limited. They include

- assisting FDA in communications with the foreign establishment,
- responding to questions concerning the foreign establishment's products that are imported or offered for import into the United States, and
- assisting FDA in scheduling inspections of the foreign establishment."

After the initial registration, firms are required to register annually, using an Annual Registration Form (FDA 2891a) mailed from the FDA. Any change in the registration status occurring between annual registrations must be submitted in a letter to the FDA within 30 days of the change.

1.2.2 Device Listing

A firm must list each classified device that it markets and submit this listing to the FDA's Device Registration and Listing Branch. The listing is not required annually. Only when significant changes occur in the device information will a firm submit a new listing form containing the changes. Please see: www.fda.gov/cdrh/devadvice/342.html#link_3 for more details.

This must be completed using a pre-printed document with an official number on it, as CDRH will not accept photocopies of Form FDA 2892. Foreign establishments that export to the US are required to list either directly, or via their US office or sole distributor. If they choose the latter route, the manufacturer must provide a "letter of authorization" to the US entity as indicated by the FDA in their guidance notes.

1.2.3 Pre-market Notification (510(k))

When marketing a device subject to pre-market notification for the first time, a firm must submit a 510(k) to the FDA at least 90 days prior to the intended marketing of the device.

A 510(k) must contain enough information to demonstrate that a device is substantially equivalent to a legally marketed device. A 510(k) is also required for a device, currently marketed or previously marketed, where there is a significant change or modification that may adversely affect the intended use, safety or effectiveness of the device. Section 513(i) of the act defines the term "substantially equivalent" as a device that:

"(1) has the same intended use and the same technological characteristics as a legally marketed device; or

(2) has the same intended use and different technological characteristics, but there is information in the 510(k) demonstrating that the device is as safe and effective as a predicate device, and the device does not raise different questions of safety and effectiveness."

The following information should be included in a 510(k):

- Name of the device;
- Establishment registration number;
- Class of the device;
- (for Class II devices) measures to comply with any applicable Special Controls;
- Adequate labeling to describe the intended use of the device;

- Information concerning the device's safety and effectiveness;
- (for Class III devices) a summary of all adverse safety and effectiveness data;
- Supporting documentation indicating that the device is similar to, or different from, comparable devices on the market;
- (for devices that have undergone changes or modifications) the effect of modifications on the safety and effectiveness of the device; and
- Additional specific information requested by the FDA.

Part 807.87 of 21 CFR (Code of Federal Regulations) sets out the information that must be contained in a 510(k) submission and www.fda.gov/cdrh/devadvice/314.html provides extensive detailed guidance.

510(k) Review Fees

The Medical Device User Fee and Modernization Act (MDUFMA) of 2002 has introduced User Fees for 510(k) and PMA applications (please see later section on MDUFMA). This means for FY2005 (October 1, 2004 to September 30, 2005) applicants will have to pay upfront: **US$3,502**. Canadian firms may qualify for small business discounts on the fees. Please refer to Appendix 7 of this guide for information provided by the FDA.

"When to Pay

Payment must be received at or before the time the 510(k) submission is submitted. If the submitter has not paid all fees owed, FDA will consider the submission incomplete and will not accept it for filing."

The following exemptions or waivers apply and is taken directly from Device Advice at www.fda.gov/cdrh/devadvice/314a.html:

Fee Exemptions and Waivers (No Fee for These)	
Category	**Exemption or Waiver**
Third-party 510(k)	Exempt from any FDA fee; however, the third-party does charge a fee for its review.
Any application for a device intended solely for pediatric use.	Exempt from user fee. Please note that changing the intended use from pediatric use to adult use requires the submission of a new 510(k). The new 510(k) is subject to the 510(k) review fee at the time of submission.
Any application from a State or Federal Government entity.	Exempt from any fee unless the device is to be distributed commercially.

1.2.4 Good Manufacturing Practices (GMP) Regulation

In December 1978, the FDA Good Manufacturing Practices (GMP) Regulation became effective. This regulation established the quality system requirements for products regulated under the FDA, including medical devices. In 1990, the Safe Medical Devices Act (SMDA) was amended, adding design to the GMP requirements that was based on ISO 9001. With the SMDA amendment, the GMP covers the design, manufacture, packaging, labeling, storage, installation and servicing of all finished medical devices intended for human use. FDA guidance for manufacturers is provided in the form of an inch-thick, crucial document entitled 'Medical Device Quality Systems Manual: A Small Entity Compliance Guide,' which relates every aspect of GMP back to the Quality System Regulation (QSR) 21 CFR 820. (Please note that GMP is also known as the QSR by the FDA and other observers. 21 CFR 820 has the legal status of prima facie evidence of the text of the original documents whereas the QSR Manual is, in effect, guidance. The manual is very readable and includes many useful examples of what is required.) Please see Section 2 of this chapter for more details and review the Device Advice at:

www.fda.gov/cdrh/devadvice/32.html

This is considered essential reading for all those interested in the detailed quality system requirements.

The FDA monitors compliance with the GMP regulation during inspections of the firm's manufacturing facility. The FDA has produced insights on this in the Chapter 18 Factory Inspections of the *Medical Device Quality Systems Manual: A Small Entity Compliance Guide*, which covers preparing for an FDA inspection.

The GMP page at CDRH has a number of useful references and training material. Please see

www.fda.gov/cdrh/gmp/gmp.html

This includes the 'Guide to Inspections of Quality Systems,' (QSIT) published in August 1999, which has five main sections: management controls, design controls, corrective and preventive actions (CAPA), production and process controls (P&PC) and sampling plans. There are also links to several presentations that are useful in improving understanding of FDA's approach.

1.3 Investigational Device Exemption (IDE)

To permit devices to be shipped for the sole purpose of investigational use on a human, the FDA can exempt manufacturers from certain requirements. This exemption is known as an Investigational Device Exemption (IDE) and applies only to investigational studies intended to collect safety and effectiveness data for medical devices when used on humans.

If a device is considered to present a significant risk, IDE applicants must submit information to

the FDA demonstrating that testing will be supervised by an Institutional Review Board (IRB), that appropriate informed consent will be obtained, and that certain records and reports will be maintained. For a non-significant risk device, submission to the FDA is not required, but IRB approval is.

Certain types of devices are exempt from the IDE regulation. These include custom devices, certain in vitro diagnostic devices, devices destined solely for veterinary use, and devices that are substantially equivalent to preamendment devices used for the same purpose.

For more detail please see www.fda.gov/cdrh/devadvice/ide/index.shtml that also helps you to link other parts of FDA regulation together.

All aspects of IDEs and related activities are subject to monitoring. The FDA has within the Office of Compliance a Bioresearch Monitoring group whose activities are often referred to as 'BIMO.' The regulations enforced by the bioresearch monitoring program for medical devices can be found in the following CFRs:

- 21 CFR 812, *Investigational Device Exemptions*, covers the procedures for the conduct of clinical studies with medical devices including application, responsibilities of sponsors and investigators, labeling, records, and reports.
- 21 CFR 50, *Protection of Human Subjects*, provides the requirements and general elements of informed consent.
- 21 CFR 56, *Institutional Review Boards*, covers the procedures and responsibilities for institutional review boards (IRBs) that approve clinical investigations protocols.
- 21 CFR 54, *Financial Disclosure by Clinical Investigators*, covers the disclosure of financial compensation to clinical investigators, which is part of FDA's assessment of the reliability of the clinical data.
- 21 CFR 820 Subpart C, *Design Controls of the Quality System Regulation*, provides the requirement for procedures to control the design of the device in order to ensure that the specified design requirements are met.
- 21 CFR 58 – Good Laboratory Practice (GLP) for Nonclinical Laboratory Studies (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=58)

1.4 Pre-market Approval

Pre-market approval (PMA) permits an applicant to market a particular medical device. PMA requirements apply to Class III devices. PMA requirements differ between preamendment and postamendment devices.

“Preamendment devices” refers to devices placed on the market prior to May 28, 1976. If the FDA determines, through an examination of a manufacturer’s 510(k) submission, that the device is substantially equivalent to a preamendment device, a PMA will not be required. However, the FDA has the power to “call for” PMAs for preamendment devices, if needed to assess the device.

“Postamendment devices” refers to devices marketed on or after May 28, 1976. The manufacturer of a Class III postamendment device that is not substantially equivalent to a preamendment Class III device is required to have a PMA application approval before marketing the device. For a device that is similar to a preamendment Class III device, for which a PMA has not been called, a 510(k) should be submitted. If, after reviewing the 510(k), the FDA determines that the device is substantially equivalent to the preamendment device, it will be subject to the same requirements as the preamendment device. If the device is not substantially equivalent to the preamendment Class III device, by statute, a PMA is required. Alternatively, a firm may choose to petition to reclassify the device to Class I or II.

As indicated earlier in this section Device Advice www.fda.gov/cdrh/devadvice/pma/ provides a useful summary of regulatory and quality requirements. The main CFRs that apply are

21 CFR 814 Pre-market Approval of Medical Devices

21 CFR 54 Financial Disclosure by Clinical Investigators

21 CFR 801 Labeling

21 CFR 820 Quality System Regulation

The review of a PMA is a four-step review process:

1. Administrative and limited scientific review by FDA staff to determine completeness (filing review);
2. In-depth scientific, regulatory, and Quality System review by appropriate FDA personnel;
3. Review and recommendation by the appropriate advisory committee (panel review); and
4. Final deliberations, documentation, and notification of the FDA decision.

PMA Review Fees

The Medical Device User Fee and Modernization Act (MDUFMA) of 2002 has introduced User Fees for 510(k) and PMA applications (please see later section 1.5.6 on MDUFMA). This means for FY2005 (October 1, 2004 to September 30, 2005) applicants will have to pay upfront: **US$239,237**. Canadian firms may qualify for small business discounts on the fees. Please refer to Appendix 7 of this guide for information provided by the FDA.

“When to Pay

Payment must be received at or before the time the application is submitted. If the applicant has not paid all fees owed, FDA will consider the application incomplete and will not accept it for filing.”

Changes to PMAs do get expensive with 180-day Supplement fee at US$51,436 and Real-Time Supplement at US$17,225.

The following exemptions or waivers apply and are taken directly from Device Advice at www.fda.gov/cdrh/devadvice/pma/userfees.html#fees

Exemptions and Waivers

The following types of applications require no fee:

- 30 day Notices and 135 day Supplements
- Special PMA Supplements-Changes Being Affected
- Express PMA Supplements
- PMA annual reports
- Humanitarian Device Exemption (HDE)
- BLA for a product licensed for further manufacturing use only

The following exemptions or waivers apply:

Fee Exemptions and Waivers (No Fee for These)	
Category	**Exemption or Waiver**
First pre-market application (PMA, PDP, BLA, or pre-market report) from a small business.	One-time waiver of the fee that would otherwise apply.
Any application for a device intended solely for pediatric use.	Exempt from any fee. If an applicant obtains an exemption under this provision, and later submits a supplement for adult use, that supplement is subject to the fee then in effect for an original pre-market application.
Any application from a State or Federal Government entity.	Exempt from any fee unless the device is to be distributed commercially.

Note: The only real waiver open to foreign establishments is for devices solely for pediatric use.

1.5 Safe Medical Devices Act (SMDA) of 1992; FDA Modernization Act (FDAMA) of 1997 and Medical Device User Fee and Modernization Act (MDUFMA) of 2002

"The basic framework governing the regulation of medical devices is established in the Medical Device Amendments to the Federal Food, Drug, and Cosmetic (FFD&C) Act. The Medical Device Amendments were enacted on May 28, 1976. The FFD&C Act was again amended with respect to the regulation of medical devices by the Safe Medical Devices Act of 1990 and the

Medical Device Amendments of 1992. New provisions governing the export of FDA regulated products, including medical devices, were established in the FDA Export Reform and Enhancement Act of 1996. The FFD&C Act was most recently amended by the Food and Drug Administration Modernization Act of 1997 (the Modernization Act). Signed into law on November 21, 1997, the Modernization Act contained provisions related to all products under FDA's jurisdiction. This document [FDAMA] summarizes each device-related section of the Modernization Act in "plain English." It is not intended to be interpretive or to set forth Agency policy for implementation." Direct quote of Dr. Bruce Burlington, then Director of CDRH taken from www.fda.gov/cdrh/devadvice/371.html

"On October 26, 2002 the Medical Device User Fee and Modernization Act of 2002 (MDUFMA) became law. MDUFMA amends the Federal Food, Drug and Cosmetic (FFD&C) Act to provide FDA important new responsibilities, resources, and challenges. MDUFMA has three particularly significant provisions:

- User fees for pre-market reviews;
- Establishment inspections may be conducted by accredited persons (third-parties);
- New regulatory requirements for reprocessed single-use devices.

On November 7, 2002 the Center for Devices and Radiological Health created a new website at www.fda.gov/cdrh/mdufma/index.html that is dedicated to MDUFMA. Included on this website are links to reference materials and background information on MDUFMA, including a full text of the law, summary of the law, and the Legislative History of MDUFMA. In addition there is a Frequently Asked Questions (FAQ) document, which should help you address questions you may have regarding the new law. As FDA proceeds with implementation of MDUFMA, CDRH expects to update the website regularly."

Direct quote taken from www.fda.gov/cdrh/devadvice/overview.html

The SMDA sets out a number of provisions for medical devices and some have since been altered by FDAMA and MDUFMA. These are briefly described below.

1.5.1 Medical Device Reporting

Manufacturers and Distributors

Under SMDA, manufacturers and distributors must submit Medical Device Reports (MDRs) when they become aware of information that suggests that the device

> (a) Caused or contributed to a death, serious illness or serious injury; or
> (b) Malfunctioned, and there is a probability that if the malfunction were to recur, the device would cause or contribute to a death, serious injury or serious illness.

Medical device reporting requirements are similar, but not identical, to the EU's vigilance reporting requirements and Canada's mandatory reporting requirements. Note that FDAMA

revoked the need for distributors to report adverse events to the FDA and/or manufacturer. Instead, distributors must keep records of complaints and make records available to the FDA upon request.

User Facilities

Medical device user facilities (hospitals, nursing homes, ambulatory surgical facilities, and outpatient treatment and diagnostic facilities) must report incidents that suggest there is a probability that a medical device has caused or contributed to the death of a patient, or to the serious injury or serious illness of a patient.

Note that FDAMA has modified requirements on the frequency of reporting from semi-annual to annual. The report is now due on January 1 each year, although user facilities may continue to use the current semi-annual user facility report. The identity of user facilities that submit MDR reports is protected from disclosure except in connection with certain actions brought to enforce device requirements or a communication to a manufacturer of a device that is the subject of a report to the FDA of death, serious illness or injury, or other significant adverse experience.

Certification

The SMDA requirement for manufacturers, importers, distributors and user facilities to certify to the FDA the number of reports they have submitted was repealed under FDAMA Section 213.

1.5.2 Tracking Requirements

Manufacturers must have in place adequate distribution records and other methods for tracking devices that are

(a) Permanently implantable or
(b) life-sustaining or life-supporting, if used outside a use facility.

The FDA has designated devices that require tracking.

1.5.3 Removals and Corrections

Under the SMDA, manufacturers, importers and distributors must report to the FDA any removals and corrections of a device to

(a) Reduce a risk to health posed by the device or
(b) Remedy a violation of the Food, Drug and Cosmetic (FD&C) Act caused by the device that may present a risk to health.

FDAMA has repealed the requirement for reporting by distributors of any removal or correction of a device undertaken to reduce risk to health posed by the device or to remedy a violation of

the FFD&C Act that may present a risk to health. The requirement still applies to manufacturers and importers.

1.5.4 Post-market Surveillance

The manufacturer is required to undertake post-market surveillance on certain products that have been designated by the FDA as requiring post-market surveillance. The manufacturer must be proactive in gathering information on a device's performance in the marketplace, with a view to ensuring that the device's performance meets safety and effectiveness requirements and that improvements can be made where required. Similar post-market surveillance activities are required under the EU MDD and Canada's Regulations.

The FDA has the authority to recall a medical device.

1.5.5 General Information on FDAMA and Third-Party Review

More information on FDAMA can be obtained from the FDA website at http://www.fda.gov/cdrh/modact/modern.html

This includes a link to an overview (www.fda.gov/cdrh/devadvice/371.html), section-by-section guidance and advice on the implementation of third-party programs. Third-party review of some devices is allowable by the FDA for pre-market review of low- to moderate-risk devices. This program is now in operation and has been used by some manufacturers to accelerate the time to market. However, manufacturers should ensure that any third party is fully accredited by the FDA for the **specific task** to be undertaken. More than thirty guidance documents emerged from the FDAMA program, all with "The Least Burdensome Principle":

"With respect to medical devices, the FDA is directed to focus its resources on the regulation of those devices that pose the greatest risk to the public and those that offer the most significant benefits. The FDA must base its decisions on clearly defined criteria and provide for appropriate interaction with the regulated industry. The new legislation assumes that enhanced collaboration between the FDA and regulated industry will accelerate the introduction of safe and effective devices to the U.S." Quote from www.fda.gov/cdrh/devadvice/371.html.

"FDAMA did not change the statutory threshold for pre-market clearance or approval. To continue to meet this standard, while also fulfilling the intent of the least burdensome provisions of FDAMA, we intend to apply the following basic principles:

- The basis for all regulatory decisions will be found in sound science and the spirit and the letter of the law;
- Information unrelated to the regulatory decision should not be part of the decision-making process;

- Alternative approaches to regulatory issues should be considered to optimize the time, effort, and resources involved in resolving the issue consistent with the law and regulations; and
- All reasonable measures should be used to reduce review times and render regulatory decisions within statutory timeframes."

Quote from www.fda.gov/cdrh/ode/guidance/1332.html.

All of FDAMA is potentially of relevance and to go through every point would only duplicate the FDA web site that is important to visit and keep visiting to keep up-to-date. Given below is a sample from FDAMA to encourage readers to further examine this helpful legislation. Samples taken directly from the guidance (www.fda.gov/cdrh/devadvice/371.html):

Section 201 - Early Collaboration of Data Requirements for Clinical Studies

Sponsors that intend to perform a clinical study of any Class III device or any implantable device in any class, will be given an opportunity to meet with FDA to discuss their investigational plan, including the clinical protocol, for the purpose of reaching an agreement on the investigational plan before they apply for an investigational device exemption (IDE).

A written request for this meeting from the sponsor to FDA is required. The request shall include a detailed description of the device, proposed conditions of use and a proposed investigational plan (including clinical protocol), and, if available, expected performance of the device. The FDA has 30 days to meet with the sponsor after receipt of the written request.

An official record will be made of any agreement that is reached between the sponsor and the FDA. This agreement will be binding and is not subject to change except

1) With written agreement of the sponsor; or

2) If FDA decides that a substantial scientific issue essential to determining the safety or effectiveness of the device has been identified following the initial agreement. In this case, the decision by FDA must be in writing and follow an opportunity for the sponsor to meet with the Agency to discuss the issue identified.

Section 204 - Device Standards

National and international standards can be put be put forward for recognition by FDA and used in PMA or 510(k) applications.

Section 206 - Pre-market Notification

Exemption from 510(k)

A 510(k) submission is not required for a Class I device unless the Class I device

1) Is intended for a use which is of substantial importance in preventing impairment of human health; or
2) presents a potential unreasonable risk of illness or injury.

Section 210 - Accreditation of Persons for Review of Pre-market Notification Reports

Background

The FDA is authorized to expand the scope of the existing Third Party 510(k) review program.

The FDA must accredit persons to conduct initial 510(k) reviews no later than one year after enactment. Accredited persons may not review:

1) Class III devices;

2) Class II devices that are permanent implants or life sustaining or life supporting; or

3) Class II devices which require clinical data, except the number in this group must not be more than 6% of total submissions (as defined by statute).

Following review by an accredited party, FDA must act within 30 days of receipt of the accredited party's recommendation to accept the recommendation or change the classification of the device. If FDA changes the recommendation, it will notify the applicant and the third party explaining in detail the reasons for the change.

Section 212 - Post-market Surveillance

Manufacturers will no longer be automatically required to conduct post-market surveillance studies for particular devices. Rather, FDA may order such studies to be conducted for certain Class II and Class III devices. The FDA can now order post-market surveillance for any Class II and Class III device:

- the failure of which would be reasonably likely to have serious adverse health consequences; or
- which is intended to be implanted in the human body for more than one year; or
- which is intended to be a life sustaining or life supporting device used outside a device user facility.

Section 216 - Product Development Protocol (PDP)

The FDA is no longer required to refer all PDP's to panel. The Agency now has discretion to refer a proposed protocol to an advisory panel for recommendation regarding approval before making a determination. However, FDA is required to refer the proposed protocol to the panel if requested by the submitter, unless the protocol and accompanying data substantially duplicate information that has been reviewed by the panel previously.

Section 410 - Mutual Recognition Agreements and Global Harmonization

Good Manufacturing Practices

The FDA shall ensure that the Quality Systems Regulation (Good Manufacturing Practices) conforms to the extent practicable with all or part of internationally recognized standards defining quality systems.

Section 417 – Registration of Foreign Establishments

Registration is required and the FDA must be provided with the name of the US Agent.

Section 421 - Labeling and Advertising Regarding Compliance with Statutory Requirements

repeals the restriction in Section 301(l) of the Federal Food, Drug and Cosmetic (FFD&C) Act, which prohibits reference to FDA approval in the labeling or advertising of medical devices that have an approved PMA or IDE.

1.5.6 General Information on MDUFMA

Medical Device User Fee and Modernization Act (MDUFMA) of 2002 as the name suggests is mainly concerned with user fees in relation to pre-market notifications. In the earlier sections on 510(k) Review Fees and PMA Review Fees the application fees raised by MDUFMA have been indicated and are significant for all manufacturers.

There is a useful summary of the law and requirements of MDUFMA at

www.fda.gov/cdrh/mdufma/mdufmasummary.html

This is clearly worth reading to ensure all the relevant implications are understood. This summary includes more details on payment, where and how to pay, consequences of failure to pay and so on. MDUFMA also has legislation concerning

- Inspections by Accredited Persons (Third-Party Inspections)
- Reprocessed Single-Use Medical Devices; and
- Additional Provisions that cover:
    - Post-market Surveillance
    - Third-party Review of 510(k)s
    - Debarment of Accredited Persons
    - Combination Products
    - Report on Devices Reviewed by Centers other than CDRH
    - Electronic Labeling
    - Electronic Registration
    - Intended Use Shall Be Based on Proposed Labeling
    - Modular Review
    - Internet List of Devices Exempted from 510(k)

- Provisions Relating to Devices Intended for Pediatric Use
- Provisions Relating to Breast Implants
- Identification of Device Manufacturer

In practice, the **Third-Party Inspections** are persons working in Notified Bodies (NBs) that are also Conformity Assessment Bodies (CABs) under mutual recognition agreements. It is worth noting that an inspection can be spread over time:

“A third-party inspection may be completed in stages over a two-year period, section 704(g)(6)(A)(ii). This allows an establishment to schedule a complete inspection in phases, and to coordinate those phases with other objectives, such as obtaining ISO certification. It also permits an accredited person to send specialized personnel at different times to complete an inspection. All of FDA's inspectional requirements must be met within the two-year period.”

“The intent of these provisions is to focus the use of third-party inspections on firms that operate in a global market that currently involves multiple inspection requirements.”

To qualify for inspection by a third-party the manufacturer must:

- The establishment must intend to manufacture class II or class III devices. Section 704(g) (1).
- The establishment must market a device in the United States and must market a device "in one or more foreign countries." Section 704(g) (6)(A)(iii).
- The most-recent inspection of the establishment must have been classified by FDA as "no action indicated" or "voluntary action indicated." Section 704(g)(6)(A)(i). An establishment where FDA has found more serious problems will not be eligible for third-party inspections.
- The establishment must notify FDA of its proposed selection of an accredited person and FDA determines if the establishment is eligible.

Some other selected quotes from the guidance are given here to convey some of the key points; however the guidance is worth reading by all regulatory and quality professionals interested in the US market.

“Restriction on repeated use of accredited persons instead of FDA: An establishment may not use accredited persons for more than four years (two complete third-party inspections, each completed within a two-year period) unless the establishment petitions FDA for a waiver and FDA approves the additional third-party inspection. Section 704(g)(6)(A)(iv)(I). This provision is intended to ensure periodic inspection by FDA, while avoiding penalizing companies who are prepared for an inspection before FDA can conduct it.”

“Effect of a finding of "official action indicated" following an inspection by an accredited person. If an establishment receives an "official action indicated" following an inspection by an accredited person, that establishment may use an accredited person for a subsequent inspection only if --

- The establishment is otherwise eligible for inspection by an accredited person;
- FDA issues a "written statement" that the violations that required action have been resolved; and
- Upon petition of the establishment, or FDA's own initiative, FDA informs the establishment that it has clearance to use an accredited person for inspections. If the establishment submits a petition, FDA must respond within 30 days.”

Reprocessing of Single-Use Devices

The key home page of this important topic is at: www.fda.gov/cdrh/reuse/index.html. It is a serious public health issue as reprocessing of single-use devices that is not validated can potentially put patients at risk.

FDA Talk Paper: FDA Revises Guidance on Reprocessing of Single-Use Devices, ***Revisions Clarify FDA’s Review Procedures (June 1, 2004) can be found at***

www.fda.gov/bbs/topics/ANSWERS/2004/ANS01291.html

For any manufacturer placing single-use medical devices on the US market this is all vital reading. It should help to stop non-validated and hence now illegal re-processing of single-use devices that were never designed to be re-used.

Identification of Device Manufacturer

“MDUFMA § 301(a) adds new section 502(u) to the FD&C Act, to require a device to "prominently and conspicuously" bear the name of its manufacturer. This can be in the form of a "generally recognized" abbreviation or unique symbol. FDA may waive this requirement for a device if it is "not feasible" or if it would compromise its safety or effectiveness.

A device that does not bear the name of the manufacturer when required is misbranded.

Section 502(u) goes into effect October 26, 2005 (36 months after enactment of MDUFMA), and its requirements apply only to devices "introduced . . . into interstate commerce after such effective date." See § 301(b) of MDUFMA and § 2(c) (1) of MDTCA.”

2 Quality System Regulation

Quality System Regulation covers the methods, facilities and controls used in the design, manufacture, packaging, labeling, storage, installation and servicing of all finished medical devices intended for human use.

The inclusion of design controls in the Quality System Regulation was a response to the significant number of recalls that resulted from faulty product design. The design control features of the Quality System Regulation came into effect on June 1, 1997 with no enforcement action taken until after June 1, 1998.

In developing the Quality System Regulation, the FDA made considerable efforts to harmonize with the quality system requirements of their major trading partners. Accordingly, this regulation covers the requirements of a full quality system and embodies the principles of the international quality system standard ISO 13485, which stipulates particular requirements for medical devices.

The GMP Section 1.2.4 of this chapter indicated the FDA guidance for manufacturers is the 'Medical Device Quality Systems Manual: A Small Entity Compliance Guide,' which relates every aspect of GMP back to the Quality System Regulation (QSR) 21 CFR 820.

Device Advice has a link to Quality Systems at: www.fda.gov/cdrh/devadvice/32.html that is considered vital reading for those using this guide. This includes further vital references to other FDA guidance that all manufacturers are strongly recommended to follow very closely.

For manufacturers who market to North America and/or Europe, a very useful complement to this is the work of the **Global Harmonization Task Force** (GHTF). Please see the section in the Introduction to this guide on this subject. The collective experience of many leading players in the industry and the key regulators is captured in a number of well-written documents freely available from http://www.ghtf.org. The GHTF "…was conceived in 1992 in an effort to respond to the growing need for international harmonization in the regulation of medical devices." The EU, US, Canada, Japan and Australia were the five founding members. Hence, the FDA's quality system requirements are very similar to those of Canada and the EU.

Please note the Quality System link at Device Advice does provide links to two useful comparisons:

Comparison Chart: 1996 Quality System Reg vs. 1978 Good Manufacturing Practice Reg vs. ANSI/ISO/ASQC Q9001 and ISO/DI 13485:1996

ISO 9001:2000 and FDA Quality System

These complement the earlier comparisons listed in the Introduction for EN ISO 13485: 2003 and PD ISO/TR 14969: 2004. These two standards, the QSRs, Medical Device Quality Systems Manual: A Small Entity Compliance Guide, QSIT Guide and all related guidance documents provide a comprehensive package of information that any medical device manufacturer can base a globally compliant quality system upon.

A quick reference comparison of: ISO 13485:1996, ISO 13485:2003, and the FDA Quality System Regulation can be found in Appendix 6.

2.1 FDA Inspections

The FDA does not require a manufacturer to register a quality system (a requirement of some European conformity assessment procedures). The FDA does rigorously inspect quality system requirements in the course of regular inspections of a manufacturer's facilities and the QSIT Guide is consistent with audit approaches of all major regulators. Foreign manufacturers are subject to FDA inspections.

"FDA determines compliance with the GMP requirements set forth in the Quality System (QS) regulation primarily by factory inspections."

If, during an inspection, a manufacturer is found to be noncompliant with a quality system requirement, this finding will be included in the inspector's Inspectional Observation (Form FDA 483) and reported to the manufacturer during an exit interview. The manufacturer may have the opportunity to fix the noncompliance on the spot. After leaving the premises, the FDA inspector will issue an official Establishment Inspection Report (EIR), which becomes a public document. The EIR classifies nonconformities into three categories:

(1) NAI - No Action Indicated;

(2) VAI - Voluntary Action Indicated; or

(3) OAI - Official Action Indicated.

If the inspector has a serious concern, a warning letter will be issued to the manufacturer. If the manufacturer fails to address the findings in the warning letter, the FDA may initiate legal action or for foreign manufacturers simply implement an import ban that is very effective. Where a foreign manufacturer does not permit FDA inspectors to inspect the facilities, the manufacturer's product will be considered noncompliant and an import ban implemented.

A manufacturer would be wise to correct any problems before the inspector issues the EIR. Once the noncompliance is recorded in the EIR, it becomes public and is available to customers and competitors. A manufacturer should seek clarification of the inspector's findings before the inspector departs the premises, use this feedback to develop a well-thought-out plan to correct the deficiency, and submit the plan to the FDA before the EIR is issued.

An excellent summary on "How to Pass FDA Factory Inspections" is available at www.bbriefings.com/pdf/954/MDC_techEDITED.qxp.pdf ; written by Trevor Lewis (a collaborator in this guide). This includes a suggested Inspection Procedure.

3 Information Sources

As repeatedly mentioned in this guide, the most useful FDA resource for most manufacturers is Device Advice at www.fda.gov/cdrh/devadvice/ and all the documents it

references.

International manufacturers can contact CDRH for more general information, or product specific questions at:

E-mail dsmica@cdrh.fda.gov

Fax (00)1-301-443-8818

Phone (00)1-301-443-6597

Write to us at: International Staff, Center for Devices and Radiological Health,
HFZ-220,
1350 Piccard Drive,
Rockville, MD 20850 USA

This contact point was taken from the International Issues page www.fda.gov/cdrh/international/index.html, where links to more contacts and program areas are given, including:

- Importing Medical Devices
- Third Party Review
- STED Initiative (see GHTF in the Introduction); and
- Non-US Regulatory Contacts and Useful Organizations.

Summary

1. Canada's Regulations attempt to harmonize medical device requirements with those of its major trading partners, particularly the EU and US. While these requirements are not identical to the EU and US requirements, the quality system requirements of the three jurisdictions are similar.

2. There is much commonality between the quality system requirements of the three jurisdictions. Canada has adopted ISO 13485:2003 as a Canadian National Standard and labeled it CAN/CSA-ISO 13485:2003. Europe now applies EN ISO 13485: 2003. The FDA's QSRs/GMP is fully consistent with ISO 13485: 2003, provided FDA guidance is rigorously followed.

3. The FDA sets out quality requirements for device manufacturers in the Quality System Regulation (QSRs) and ISO 13485: 2003 is consistent with the QSRs. These are verified by FDA inspectors during regular inspections of a manufacturer's facilities. Third-party audit of medical device quality systems to FDA requirements by approved bodies is now possible when certain conditions are met.

4. Health Canada has established an accreditation system with the Standards Council of Canada for Registrars (auditors) qualified to audit medical device manufacturers' quality systems. Before entering into an agreement with a Registrar, it would be wise to contact Health Canada to determine which Registrars are acceptable.

5. For all three jurisdictions, device class influences the quality system requirements. An improperly classified device can lead a manufacturer to design an inappropriate quality system. Hence, it is advisable to confirm the device class with a regulatory agency or registrar prior to designing the quality system.

6. The medical devices regulations of each jurisdiction set out a number of requirements other than quality system requirements. These include requirements pertaining to

   • Post-market surveillance;

   • Problem reporting;

   • Labeling;

   • Product recall;

   • Safety and effectiveness of the device;

   • Custom-made devices or devices for special access or emergency use; and

   • Devices used for investigational testing or clinical trials.

There are many similarities among the requirements of each jurisdiction, particularly as they relate to post-market surveillance, problem reporting and product recall. The Global Harmonization Task Force is working towards even greater use of common regulatory documentation and has largely succeeded in establishing a global quality system standard: **ISO 13485: 2003 Medical devices - Quality management systems - Requirements for regulatory purposes** that is clearly the single most important reference of this guide.

7. There are vast sources of information available from all jurisdictions pertaining to regulatory requirements. Extensive use of Canadian, FDA and European guidance documents is strongly recommended. The identification and source of these documents can be found in Chapters 1, 2 and 3 respectively.

Appendix 1: Example of European Risk Classes of Medical Devices

Class III	Class IIb
BATTERY, PACEMAKER	ANALYZER, GAS, MULTIPLE, GASEOUS PHASE (ANESTHETIC CONC.)
CATHETER, SEPTOSTOMY	PULMONARY RADIO AEROSOL DIAGNOSTIC KIT
CLIP, ANEURYSM	NEEDLE, CONDUCTION, ANESTHETIC (W/WO INTRODUCER)
CONTROLLER, CLOSED-LOOP, BLOOD PRESSURE	GAS-MACHINE, ANESTHESIA
ELECTRODE, PACEMAKER, TEMPORARY	VENTILATOR, EMERGENCY, POWERED (RESUSCITATOR)
GRAFT, BONE	STIMULATOR, ELECTRO-ACUPUNCTURE
HEART, ARTIFICIAL	ELECTROANESTHESIA APPARATUS
HEART-VALVE, MECHANICAL	MONITOR, OXYGEN (VENTILATORY) W/WO ALARM
IMPLANTED NEUROMUSCULAR STIMULATOR	METER, AIRWAY PRESSURE (INSPIRATORY FORCE)
KIT, BLOOD PRESSURE, CENTRAL VENOUS	MEMBRANE LUNG FOR LONG-TERM PULMONARY SUPPORT
LEAD, PACEMAKER, IMPLANTABLE	VENTILATOR, NON-CONTINUOUS (RESPIRATOR)

Class III	Class IIb
MATERIALS, REPAIR OR REPLACEMENT, PACEMAKER	MONITOR, BREATHING FREQUENCY
MONITOR, CEREBRAL BLOOD FLOW, THERMAL DIFFUSION	APPARATUS, AUTOTRANSFUSION
OXIMETER, INTRACARDIAC	KIT, CONDUCTION ANESTHETIC
PACEMAKER LEAD, MYOCARDIAL, IMPLANTABLE	CHAMBER, HYPERBARIC
PATCH, PERICARDIAL	VENTILATOR, CONTINUOUS (RESPIRATOR)
PROSTHESIS, VASCULAR GRAFT, OF 6MM AND GREATER DIAMETER	ANALYZER, GAS, OXYGEN, GASEOUS PHASE
RING, ANNULOPLASTY	BED, ROCKING, BREATHING ASSIST
SHIELD, CORNEAL	MONITOR (APNEA DETECTOR), VENTILATORY EFFORT
SHUNT, CENTRAL NERVOUS SYSTEM AND COMPONENTS	RESPIRATOR, NEONATAL VENTILATOR
SPONGE, HEMOSTATIC, ABSORBABLE COLLAGEN	MONITOR, RESPIRATORY
STENT, CARDIOVASCULAR	MONITOR, LUNG WATER MEASUREMENT
STIMULATOR, SPINAL CORD, IMPLANTE (PAIN RELIEF)	MONITOR, PO2, CONTINUOUS
TISSUE, HEART VALVE	ALARM, BREATHING CIRCUIT
TRANSDUCER, PRESSURE, CATHETER TIP	VENTILATOR, ANESTHESIA UNIT

Class II a	Class I
ANALYZER, GAS, HELIUM, GASEOUS PHASE	CATHETER, BRONCHOGRAPHY
MASK, GAS, ANESTHETIC	ACUPUNCTURE, ACCESSORIES
CUFF, TRACHEAL TUBE, INFLATABLE	PROTECTOR, DENTAL
FILTER, CONDUCTION, ANESTHETIC	STYLET, TRACHEAL TUBE
COMPRESSOR, AIR, PORTABLE	STRAP, HEAD, GAS MASK

Class II a	Class I
VENTILATOR, EMERGENCY, MANUAL (RESUSCITATOR)	DROPPER, ETHER
TUBE, TRACHEAL (W/WO CONNECTOR)	FORCEPS, TUBE INTRODUCTION
INTRODUCER, SPINAL NEEDLE	CLIP, NOSE
NEEDLE, ACUPUNCTURE	ALGESIMETER, MANUAL
GAUGE, GAS PRESSURE, CYLINDER/PIPELINE	FLOWMETER, CALIBRATION, GAS
STIMULATOR, NERVE, BATTERY POWERED	BOTTLE, BLOW
TRANSDUCER, GAS PRESSURE	MOUTHPIECE, BREATHING
MASK, OXYGEN	CATHETER, NASAL, OXYGEN
UNIT, LIQUID OXYGEN, PORTABLE	STETHOSCOPE HEAD
TENT, OXYGEN, ELECTRICALLY POWERED	LARYNGOSCOPE, NON-RIGID

Class II a	Class I
TUBING, PRESSURE AND ACCESSORIES	GENERATOR, OXYGEN, PORTABLE
METER, PEAK FLOW, SPIROMETRY	KIT, SUCTION, AIRWAY
CALCULATOR, PULMONARY FUNCTION INTERPRETATOR (DIAGNOSTIC)	SPREADER, CUFF
STETHOSCOPE, ESOPHAGEAL	DEVICE, FIXATION, TRACHEAL TUBE
VAPORIZER, ANESTHESIA, NON-HEATED	SUPPORT, PATIENT POSITION
REGULATOR, PRESSURE, GAS CYLINDER	BRUSH, CLEANING, TRACHEAL TUBE
FLOWMETER, TUBE, THORPE, BACK-PRESSURE COMPENSATED	SUPPORT, BREATHING TUBE
KIT, SAMPLING, ARTERIAL BLOOD	HUMIDIFIER, NON DIRECT PATIENT INTERFACE (HOME USE)
FLOWMETER, ANESTHESIA	TRACHEOTOME
TIMER, FLOW	CALIBRATOR, ANESTHESIA UNIT

Appendix 2: Questions for the Notified Body/Registrar

1. What is the scope of your accreditation? Does accreditation cover our products?
2. Is your organization accredited to register a quality system to ISO 13485, under the Canadian Medical Devices Conformity Assessment System (CMDCAS)?
3. What medical devices' companies has your organization audited and certified to ISO 13485:2003 and CE Mark (where applicable)?
4. How familiar are your auditors with the requirements for our products? Would these auditors be assigned to this registration process?
5. Do you subcontract any registration-related activities to other organizations? If so, what activities and to whom are these subcontracted?
6. If applicable, how do you assure the quality of subcontracted services?
7. If a CE Mark audit, does your company work with a Canadian affiliate?
8. In registering our company to CE Mark, will we also receive a certification of registration to ISO 13485? Will there be an extra cost for this? If so how much?
9. Do you offer information sessions with clients?
10. What is the application process?
11. What are your criteria for recommending a client for registration? Define terms such as, *major* and *minor nonconformances.*
12. What is your reassessment or on-going surveillance process? Are there any particular standards that are subject to review at every reassessment?
13. How long are the CE Mark and other certifications valid?
14. How do you assure continuity between the initial assessment and the surveillance assessment?
15. What fees, expenses or other charges are typically associated with registration and surveillance visits?
16. What are your required lead times for the various stages in the registration and surveillance process?
17. Are there any additional charges that might result from a delay in the assessment, because of an identified need to further develop the quality system before continuing?

The Selection Process

- Four notified bodies/registrars are being invited to submit proposals for this registration.
- Notified bodies/registrars will be assessed against the criteria embodied in the above questions. Familiarity with our business, timing, cost, receiving additional registration certificates and proximity to our operation will be major considerations in the selection process.
- Additional information may be requested at a later date, including a possible meeting.

Appendix 3: Content of a Design Dossier

The MDD provides the following information on what must be included in the design dossier:

1. A description of the design, manufacture, and performance of the device to include documents needed to assess whether the device conforms to the requirements of the MDD (Annex II, 4.2 and 3.2 (c))
2. A general description of the device, including any variants planned.
3. The design specifications, including the standards which have been applied and the results of the risk analysis, as well as a description of the solutions adopted to fulfill the ERs (essential requirements) which apply to the devices if the standards referred to in Article 5 of the MDD are not applied in full.
4. The techniques used to control and verify the design and the processes and systematic measures which will be used when the devices are being designed.
5. If the device is to be connected to other devices in order to operate as intended, proof must be provided that it conforms to the ERs when connected to any such devices having the characteristics specified by the manufacturer.
6. A statement indicating whether or not the device incorporates, as an integral part, a substance as referred to in Section 7.4 of Annex 1 of the MDD and data on the tests conducted in this connection.
7. The clinical data referred to in Annex X of the MDD.
8. The draft label and, where appropriate, instructions for use.

The following should be considered as part of the design dossier where appropriate:

9. A statement under which directive the submission is being made.
10. The name of the device family.
11. The name and address of the manufacturer.
12. Classification of the device/family giving the details of which classification rules apply.
13. Complete ERs checklist referring to the means by which compliance has been achieved.
14. A statement regarding Annex II, 3.2(c), 4th indent (connections to other devices).
15. A statement regarding Annex I, 7.4/Annex II, 3.2 (c), 5th indent (incorporation of medical devices).
16. A statement regarding any previous marketing history, if the device/family has been marketed elsewhere, if appropriate.
17. Device description and indications of use, including drawings and technical design features.
18. Catalogue numbers and descriptions.
19. Materials used in the device and manufacturing process.
20. Manufacturing method.
21. Packaging details.
22. Text for the label and instructions for use.
23. Bioburden, sterilization method and validation, and microbiological testing (Annex II, 3.2

(d)).
24. In-process and final device testing methods, limits and frequency (Annex II, 3.2 (e)).
25. Biological safety evaluation.
26. Risk analysis.
27. Clinical evaluation.
28. If a device/family has previously been marketed, a brief statistical summary of incidents.
29. Any appropriate and relevant certification of approvals

It is strongly recommended that manufacturers ask their selected Notified Body for guidance on the expected contents of the design dossier for specific devices as early as possible in the accreditation process. Many have suggested contents for technical documentation and related presentations to assist in this process.

Appendix 4: EUCOMED Guidance Notes on the Interpretation of the Essential Requirements.

Essential Requirement	Guidance
1. GENERAL REQUIREMENTS 1. The devices must be designed and manufactured in such a way that, when used under the conditions and for the purposes intended, they will not compromise the clinical condition or the safety of patients, or the safety and health of users or, where applicable, other persons, provided that any risks which may be associated with their use constitute acceptable risks when weighed against the benefits to the patient and are compatible with a high level of protection of health and safety.	Requirements 1 and 2 require the device to be safe and useful. In practice, this is likely to involve a different approach for new (or recently introduced) products and established products. In the case of new products, a manufacturer would typically (I) review the design brief and the design solutions represented in the product specification. This will include a risk assessment in line with the harmonized standard. (II) review published literature and his own experience of similar devices. (III) assess compliance of the product and its packaging to his own specifications and to published standards. (IV) review labeling and (where appropriate) instructions for use (V) review final release procedures for commercial distribution for the product. In the case of established products, point (iii) above will be relevant. For the rest, the manufacturer is likely to rest on a review of his complaints history for the product in question. The 8th recital in the directive makes clear that all the above analyses (and indeed those suggested in the rest of this document) would have full regard to technical and economic considerations.
2. The solutions adopted by the manufacturer for the design and construction of the devices must conform to safety principles, taking account of the generally acknowledged state of the art. In selecting the most appropriate solutions, the manufacturer must apply the following principles in the following order: • eliminate or reduce risks as far as possible (inherently safe design	Need to use harmonized standards note: EN 1441: 1998 Medical devices – risk analysis; is replaced by: EN 14971: 2001 Medical devices – Application of risk management to medical devices.

Essential Requirement	Guidance
and construction), • where appropriate take adequate protection measures including alarms if necessary, in relation to risks that cannot be eliminated, • inform users of the residual risks due to any shortcomings of the protection measures adopted.	
3. The devices must achieve the performance intended by the manufacturer and be designed, manufactured, and packaged in such a way that they are suitable for one or more of the functions referred to in Article I (2) (a), as specified by the manufacturer.	This is a performance requirement. The manufacturer will need to have evidence that the device complies with his specified requirements. Any test regime should reflect this. Where the manufacturer is operating a quality system to Annexes II, V, or VI of the Directive, this essential requirement will already be addressed at least in part (Annexes II, V and VI require in effect certification against EN29001, 29002 and 29003 respectively). Now use EN 13485: 2003 and other harmonized standards.
4. The characteristics and performances referred to in Sections 1, 2 and 3 must not be adversely affected to such a degree that the clinical condition and safety of the patients and, where applicable, of other persons are compromised during the lifetime of the device as indicated by the manufacturer, when the device is subjected to the stresses which can occur during normal conditions of use.	The manufacturer should be able to demonstrate that he has identified the stresses which occur during the normal conditions of use intended by the manufacturer during the lifetime of the device as expected or indicated by the manufacturer. He must then consider any adverse effects and assess whether these are acceptable. The lifetime of the device can be considered to include the period prior to the first use, and the period or number of uses expected or recommended by the manufacturer. In practice, such assessments will normally be done by appropriate bench testing, simulated shelf life testing and clinical evaluation if applicable. For established products, the manufacturer would normally rely on a review of complaints history.
5. The devices must be designed, manufactured and packed in such a way that their characteristics and performances during their intended use will not be adversely affected during transport and storage taking account of the instructions and information provided by the manufacturer.	The manufacturer should be able to demonstrate that he has identified the stresses that can occur during transport or storage in accordance with any instructions for use and information provided by the manufacturer (see 13.3 I below), and adequately addressed those in the design and testing of the device and its packaging. Again for established products, the manufacturer will normally rely on a review of complaints history.
6. Any undesirable side effects must constitute an acceptable risk when weighed against the performances intended.	This requires identification of undesirable side effects. For new or significantly modified products the manufacturer will be expected to perform

Essential Requirement	Guidance
	and act upon a risk analysis. For well-established products, the manufacturer will be expected to have acted upon experience in use. The manufacturer must ensure that the side effects are not out of proportion to the performances intended by the manufacturer. The analysis which the manufacturer is expected to make must not be confused with the judgement that each user must make as to whether the use of a particular device is justified in the particular clinical circumstances.
REQUIREMENTS REGARDING DESIGN AND CONSTRUCTION 7. Chemical, physical and biological properties. 7.1 The devices must be designed and manufactured in such a way as to guarantee the characteristics and performances referred to in Section I on the "General Requirements". Particular attention must be paid to: • the choice of materials used, particularly as regards toxicity and where appropriate, flammability; • the compatibility between the materials used and biological tissues, cells and body fluids, taking account of the intended purpose of the device;	The manufacturer should be able to demonstrate that he has chosen materials which are appropriate, given the intended purpose of the device. The risk of toxicity, flammability and bio-compatibility, should be examined and may call for particular labeling or instructions for use. Examination of these should have been included in the risk analysis. The manufacturer will often have historic data on materials used in similar products, and this should be reviewed. A biological safety evaluation should be made in accordance with relevant standards, though here again it may well be possible to limit testing by having due regard for past tests on the same or similar materials used for the same or similar applications.
7.2 The devices must be designed, manufactured and packed in such a way as to minimize the risk posed by contaminants and residues to the persons involved in the transport, storage and use of the devices and to the patients, taking account of the intended purpose of the product. Particular attention must be paid to the tissues exposed and to the duration and frequency of the exposure.	Any contaminants and residues in or on the device which could cause significant adverse effects should be identified. This would include solvents; process, (including sterilization), residues; mould release agents; particulate contamination; fluid spillage in the case of medical electrical equipment. Once identified, the potential risk to patients or others should be considered and reduced so far as is practicable. Particular labeling or instructions may be called for.
7.3 The devices must be designed and manufactured in such a way that they can be used safely with the materials, substances and gases with which they enter into contact during normal use or during routine procedures; if the devices are intended to administer medicinal products they must be designed and manufactured in such a way as to be compatible with the medicinal products concerned according to the provisions and restrictions governing those products and that their performance is maintained in accordance with	Evidence will be needed that foreseeable interactions with materials, substances and gases in normal use have been examined. If it is probable that under the intended conditions of use the device may come into contact with materials with which it is incompatible, appropriate warnings must be included in the labeling or instructions for use. Where the device is intended by the manufacturer to be cleaned or disinfected or sterilized, suitable materials should be specified. The effect of ingress of liquids and gases

Essential Requirement	Guidance
the intended use.	during these procedures will need to considered. This may call for particular instructions in the documentation supplied with the product.
7.4 Where a device incorporates, as an integral part, a substance which, if used separately, may be considered to be a medicinal product as defined in Article I of Directive 65/65/EEC and which is liable to act upon the body with action ancillary to that of the device, the safety, quality and usefulness of the substance must be verified, taking account of the intended purpose of the device, by analogy with the appropriate methods specified in Directive 75/318/EEC.	This requirement does not relate to cases where such a substance is used merely, for example, to modify the surface characteristics of a device, but which is not systemically available and cannot be shown of itself to be likely to have any biological action on the patient. Generally a manufacturer will identify tests for materials (including relevant tests in EN 30993 Biological testing of medical devices) which are analogous to the tests indicated in 75/318/EEC in the sense that they achieve for his product an appropriate assurance that the device when used as intended will not give rise to an unacceptable level of side effect. Now use EN 10993 series where appropriate. The manufacturer will normally have regard to any pharmacopoalal monographs relating to the substances in question (particularly those published in Ph.Eur.; U.S.P.; and B.P.)and substances which conform to such monographs would be presumed to be of appropriate quality. The utility of the substance will normally be apparent from the manufacturer's design verification.
7.5 The devices must be designed and manufactured in such a way as to reduce to a minimum the risks posed by substances leaking from the device.	"Leaking" includes leaching. Risks include those to patients and other persons.
7.6 The devices must be designed and manufactured in such a way as to reduce as much as possible, risks posed by the unintentional ingress of substances into the device taking into account the device and the nature of the environment in which it is intended to be used.	This is the counterpart of 7.5. It should include, for example, reduction of the risk of air leaking into infusion apparatus. Both this and the previous essential requirement will normally be addressed by appropriate bench testing and biological safety testing and (if applicable) by clinical evaluation.
8. <u>Infection and microbial contamination</u> 8.1 The devices and their manufacturing processes must be designed in such a way as to eliminate or reduce as far as is possible the risk of infection to the patient, user and third parties. The design must allow easy handling and, where necessary, minimize contamination of the device by the patient or vice versa during use.	Much if not all of this essential requirement will have been addressed by the work done to meet the general requirements 1-6 above. Of particular relevance will be sterilization validation reports and bioburden data. Single use sterile products should be presented so far as is practicable in a form which facilitates aseptic presentation for use.
8.2 Tissues of animal origin must originate from animals that have been	Paragraph 1 of this essential requirement may often go beyond what is

Essential Requirement	Guidance
subjected to veterinary controls and surveillance adapted to the intended use of the tissues. Notified bodies shall retain information on the geographical origin of the animals. Processing, preservation, testing and handling of tissues, cells and substances of animal origin must be carried out so as to provide optimal security. In particular safety with regard to viruses and other transferable agents must be addressed by implementation of validated methods of elimination or viral inactivation in the course of the manufacturing process.	practicable for particular materials derived from animal tissue e.g. heparin. It may also be wholly excessive for other materials such as beeswax, silk or lanolin. Accordingly, if should be interpreted in the context of each particular case. What may be appropriate is to request certificates of origin from suppliers of animal origin which could be associated with a substantial risk of infection or adverse reactions. It is in relation to such materials that the manufacturer or his supplier should review his handling and processing procedures. Useful guidance as to the materials of animal origin in relation to which viral inactivation measures are likely to be required is given in the UK Department of Health publication "Animal Tissues in Medical Devices: Guidance on the Control of Source Materials and the Validation and Routine Control of Chemical Methods used for Sterilization". The **Animal Tissues Directive** (2003/32/EC) of 23 April 2003 introduced detailed specifications with respect to medical devices manufactured utilizing tissues of animal origin. Vital to use: • EN 12442-1:2000 Animal tissues and their derivatives utilized in the manufacture of medical devices. Analysis and management of risk. • EN 12442-2:2000 Animal tissues and their derivatives utilized in the manufacture of medical devices. Controls on sourcing, collection and handling. • EN 12442-3:2000 Animal tissues and their derivatives utilized in the manufacture of medical devices. Validation of the elimination and/or inactivation of viruses and transmissible agents.
8.3 Devices delivered in a sterile state must be designed, manufactured and packed in a non-reusable pack and/or according to appropriate procedures to ensure that they are sterile when placed on the market and remain sterile, under the storage and transport conditions laid down, until the protective packaging is damaged or opened.	Use harmonized standards where possible, especially EN 868-1: Packaging materials and systems for medical devices which are to be sterilized – Part 1: general requirements and test methods.
8.4 Devices delivered in a sterile state must have been manufactured and sterilized by an appropriate, validated method.	The European sterilization standards apply. This includes EN 556-1: 2001 Sterilization of medical devices. Requirements for medical devices to be

Essential Requirement	Guidance
	designated "STERILE". Requirements for terminally sterilized medical devices and EN 556-2: 2003 Sterilization of medical devices. Requirements for medical devices to be designated "STERILE". Requirements for aseptically processed medical devices.
8.5 Devices intended to be sterilized must be manufactured in appropriately controlled (e.g., environmental) conditions.	It is important to interpret this essential requirement in the context of each particular manufacturer's product range and manufacturing process. The extent to which it is necessary or practicable to control the manufacturing environment will vary, and the manufacturer should be allowed flexibility in the choice of method to achieve bioburden and/or particulate levels appropriate to the particular products in question.
8.6 Packaging systems for non-sterile devices must keep the product without deterioration in the level of cleanliness stipulated and, if the devices are to be sterilized prior to use, minimize the risk of microbial contamination. The packaging system must be suitable taking account of the method of sterilization indicated by the manufacturer.	Use harmonized standards where possible, especially EN 868-1: Packaging materials and systems for medical devices which are to be sterilized – Part 1: general requirements and test methods.
8.7 The packaging and/or label of the device must distinguish between identical or similar products sold in both sterile and non-sterile condition.	Sterile devices are required by essential requirement 13.3 (c) to be labelled “STERILE”. Products not so labelled will therefore be considered to be non-sterile. A manufacturer need only label a device “non-sterile” if he himself produces both sterile and non-sterile versions of the same device such that there might otherwise be confusion. Products made by competitors will have a different trademark and get-up and will therefore not be confused with his own products. In any event, it is impracticable for a manufacturer to be expected to know if other manufacturers have on the market or introduce a “sterile” product similar to his own “non-sterile” product.
9. <u>Construction and environmental properties.</u> 9.1 If the device is intended for use in combination with other devices or equipment, the whole combination, including the connection system must be safe and must not impair the specified performance of the devices. Any restrictions on use must be indicated on the label or in the instruction for use.	The work done to address the general essential requirements 1-6 above will normally cover this essential requirement in particular through the reviews of the labeling and the compatibility with other products or materials indicated above.
9.2 Devices must be designed and manufactured in such a way as to remove or minimize as far as is possible:	The first and second indents are, for medical electrical equipment, covered by the EN60601 series.

Essential Requirement	Guidance
• the risk of injury, in connection with their physical features, including the volume/pressure ratio, dimensional, and where appropriate ergonomic features, • risks connected with reasonably foreseeable environmental conditions, such as magnetic fields, external electrical influences, electrostatic discharge, pressure, temperature or variations in pressure and acceleration, • the risks of reciprocal interference with other devices normally used in the investigations or for the treatment given, • risks arising where maintenance or calibration are not possible (as with implants), from ageing of materials used or loss of accuracy of any measuring or control mechanism.	The third indent will be covered by the EN60601 collateral standard on EMC. The fourth indent only applies where maintenance or calibration are impossible i.e. an implanted device.
9.3 Devices must be designed and manufactured in such a way as to minimize the risks of fire or explosion during normal use and in single fault condition. Particular attention must be paid to devices whose intended use includes exposure to flammable substances which could cause combustion.	EN60601-1 covers medical electrical equipment for use in flammable atmospheres, however if does not cover oxygen enriched atmospheres. Any special requirement should be covered by the relevant EN60601 Part 2.
10. Devices with a measuring function 10.1 Devices with a measuring function must be designed and manufactured in such a way as to provide sufficient accuracy and stability within appropriate limits of accuracy and taking account of the intended purpose of the device. The limits of accuracy must be indicated by the manufacturer.	This requirement means that the device must perform according to the manufacturers specification, and that the choice of that specification of accuracy and stability will be justified in the technical documentation, or as required by the relevant EN60601 Part 2.
10.2 The measurement, monitoring and display scale must be designed in line with ergonomic principles, taking account of the intended purpose of the device.	Consideration of the ergonomics of the display will need to be demonstrated in the design documentation.
10.3 The measurements made by devices with a measuring function must be expressed in legal units conforming to the provisions of Council Directive 80/181/EEC, as last amended by Directive 89/617/EEC.	The choice of units is covered by EN60601 series for medical electrical equipment.
11. Protection against radiation 11.1 General 11.1.1 Devices shall be designed and manufacturer such that exposure of	Note that this covers all forms of radiation e.g. light, radio frequency and heat. Medical electrical equipment are covered by the EN60601 series.

Essential Requirement	Guidance
patients, users and other persons to radiation shall be reduced as far as possible compatible with the intended purpose, whilst not restricting the application of appropriate specified levels for therapeutic and diagnostic purposes.	
11.2 Intended radiation 11.2.1 Where devices are designed to emit hazardous levels of radiation necessary for a specific medicinal purpose the benefit of which is considered to outweigh the risks inherent in the emission, it must be possible for the user to control the emissions. Such devices shall be designed and manufactured to ensure reproducibility and tolerance of relevant variable parameters.	This requirement should be covered by EN60601-1-3 for diagnostic X-ray equipment and the relevant EN60601 Part 2s for other equipment.
11.2.2 Where devices are intended to emit potentially hazardous, visible and/or invisible radiation, they must be fitted, where practicable, with visual displays and/or audible warnings of such emissions.	Use harmonized standards to gain presumption of compliance wherever possible. This means the manufacturer must be able to prove compliance by testing, preferably independent testing.
11.3 Unintended radiation 11.3.1 Devices shall be designed and manufactured in such a way that exposure of patients, users and other persons to the emissions of unintended, stray or scattered radiation is reduced as far as possible.	Note that this requirement is addressed to all forms of radiation. This requirement should be by EN60601-1 and also the relevant EN60601 Part 2s.
11.4 Instructions 11.4.1 The operating instructions for devices emitting radiation must give detailed information as to the nature of the emitted radiation, means of protecting the patient and the user and on ways avoiding misuse and of eliminating the risks inherent in installation.	This requirement should be covered by EN60601-1 and the relevant Part 2s.
11.5 Ionizing radiation 11.5.1 Devices intended to emit ionizing radiation must be designed and manufactured in such a way as to ensure that, where practicable, the quantity, geometry and quality of radiation emitted can be varied and controlled taking into account the intended use.	Use harmonized standards to gain presumption of compliance wherever possible. This means the manufacturer must be able to prove compliance by testing, preferably independent testing.

Essential Requirement	Guidance
11.5.2 Devices emitting ionizing radiation intended for diagnostic radiology shall be designed and manufactured in such a way as to achieve appropriate image and/or output quality for the intended medical purpose whilst minimizing radiation exposure of the patient and user.	Use harmonized standards to gain presumption of compliance wherever possible. This means the manufacturer must be able to prove compliance by testing, preferably independent testing.
11.5.3 Devices emitting ionizing radiation, intended for therapeutic radiology shall be designed and manufactured in such a way as to enable reliable monitoring and control of the delivered dose, the beam type and energy and where appropriate the quality of radiation.	Use harmonized standards to gain presumption of compliance wherever possible. This means the manufacturer must be able to prove compliance by testing, preferably independent testing.
12. Requirements for medical devices connected to or equipped with an energy source. 12.1 Devices incorporating electronic programmable systems must be designed to ensure the repeatability, reliability and performance of these systems according to the intended use. In the event of a single fault condition (in the system) appropriate means should be adopted to eliminate or reduce as far as possible consequent risks.	This requirement will be covered by EN60601-1-4.
12.2 Devices where the safety of the patients depends on an internal power supply must be equipped with a means of determining the state of the power supply.	This requirement will be covered by the relevant EN60601 Part 2s.
12.3 Devices where the safety of the patients depends on an external power supply must include an alarm system to signal any power failure.	This requirement will be covered by the relevant EN60601 Part 2s.
12.4 Devices intended to monitor one or more clinical parameters of a patient must be equipped with appropriate alarm systems to alert the user of situations which could lead to death or severe deterioration of the patient's state of health.	This requirement will be covered by the relevant EN60601 Part 2s.
12.5 Devices must be designed and manufactured in such a way as to minimize the risks of creating electromagnetic fields which could impair the operation of other devices or equipment in the usual environment.	This requirement will be covered by EN60601-1-2 and by the relevant EN60601 Part 2s.
12.6 Protection against electrical risks	This requirement is covered by EN60601-1 and the relevant EN60601 Part 2s.

Essential Requirement	Guidance
Devices must be designed and manufactured in such a way as to avoid, as far as possible, the risk of accidental electric shocks during normal use and in single fault condition, provided the devices are installed correctly.	
12.7 Protection against mechanical and thermal risks 12.7.1 Devices must be designed and manufactured in such a way as to protect the patient and user against mechanical risks connected with, for example, resistance, stability and moving parts.	"Resistance" in this context means resistance to breakage e.g. "Strength". Covered for medical electrical equipment by EN60601-1 and any relevant EN60601 Part 2s.
12.7.2 Devices must be designed and manufactured in such a way as to reduce to the lowest possible level the risks arising from vibration generated by the devices, taking account of technical progress and of the means available for limiting vibrations, particularly at source, unless the vibrations are part of the specified performance.	This requirement should be interpreted in the context of particular products. The second amendment to EN60601-1 will specify limits which may be amended by any relevant EN60601 Part 2s. In many devices, vibration is unlikely adversely to affect the patient and in other cases it may be precisely intended that the device vibrates. In other cases (e.g. an operating table) it may be critical to avoid vibration. It may also be necessary to avoid vibration which could adversely affect the user.
12.7.3 Devices must be designed and manufactured in such a way as to reduce to the lowest possible level the risks arising from the noise emitted, taking account of technical progress and of the means available to reduce noise, particularly at source, unless the noise emitted is part of the specified performance.	Hazardous levels of noise are defined in ISO standards, however it is extremely unlikely that any medical device would approach such levels. Certain equipment will for medical reasons require limits for low noise e.g. baby incubators. If necessary these limits will be defined in the appropriate EN60601 Part 2s. Where alarms are fitted, the EN for Audible Alarms will specify minimum sound levels.
12.7.4 Terminals and connectors to the electricity, gas or hydraulic and pneumatic energy supplies which the user has to handle must be designed and constructed in such a way as to minimize all possible risks.	This requirement is covered generally for medical electrical equipment by EN60601 and specifically by any relevant EN60601 Part 2s.
12.7.5 Accessible parts of the devices (excluding the parts or areas intended to supply heat or reach given temperatures) and their surrounding must not attain potentially dangerous temperatures under normal use.	This requirement should be interpreted in the context of particular devices and for some devices may be impossible to satisfy, e.g. cautery, radiant heat lamps. This essential requirement obviously excludes devices or parts of them intended to supply heat. Any hazards to the environment, unless specifically covered by EN60601-1 and any relevant Part 2s, should be covered by labeling and warnings.
12.8. Protection against the risks posed to the patient by energy supplies or	This essential requirement only applies to devices intended to supply the

Essential Requirement	Guidance
substances 12.8.1. Devices for supplying the patient with energy or substances must be designed and constructed in such a way that the flow-rate can be set and maintained accurately enough to guarantee the safety of the patient and of the user.	patient with energy or substances, the rate of which can be adjusted. Even if absolute accuracy were assured this would not guarantee the safety of the patient and user. EN60601-1 and any relevant EN60601 Part 2s apply.
12.8.2 Devices must be fitted with the means of preventing and/or indicating any inadequacies in the flow-rate which could pose a danger. Devices must incorporate suitable means to prevent, as far as possible, the accidental release of dangerous levels of energy from an energy and/or substance source.	This requirement is covered generally by EN60601-1 and specifically by the relevant EN60601 Part 2s.
12.9 The function of the controls and indicators must be clearly specified on the devices. Where a device bears instructions required for its operation or indicates operating or adjustment parameters by means of a visual system, such information must be understandable to the user and, as appropriate, the patient.	This requirement only applies to adjustable controls (i.e. not internal control mechanisms). Covered generally by EN60601-1 and specifically by any relevant EN60601 Part 2s.
13. Information supplied by the manufacturer 13.1 Each device must be accompanied by the information needed to use it safely and to identify the manufacturer, taking account of the training and knowledge of the potential users. This information comprises the details on the label and the data in the instructions for use. As far as practicable and appropriate, the information needed to use the device safely must be set out on the device itself and/or on the packaging for each unit or, where appropriate, on the sales packaging. If individual packaging of each unit is not practicable, the information must be set out in the leaflet supplied with one or more devices.	Guidance as to interpretation of the essential requirements relating to labeling and instructions for use is to be found in the EUCOMED document entitled "Guidance on interpretation of requirements relating to labeling and instructions for use". This should be read alongside the harmonized labeling standard (currently prEN1041) and for medical electrical equipment EN60601-1 when amended by the second amendment. The EUCOMED document also includes illustrative examples of labeling which would comply with the directive. EN 1041: 1998 Information supplied by the manufacture with medical devices; is a useful well established harmonized standard. Use harmonized standards to gain presumption of compliance wherever possible. This means the manufacturer must be able to prove compliance by testing, preferably independent testing. There are standards for specific

Essential Requirement	Guidance
Instructions for use must be included in the packaging for every device. By way of exception, no such instructions for use are needed for devices in Class I or II a if they can be used safely without any such instructions.	products, including in vitro diagnostic (IVD) devices. Self use/test device labeling needs to be tested.
13.2 Where appropriate, this information should take the form of symbols. Any symbol or identification colour used must conform to the harmonized standards. In areas for which no standards exist, the symbols and colours must be described in the documentation supplied with the device.	EN 980: 2003 Graphical symbols for use in the labeling of medical devices; is a useful well established harmonized standard.
13.3 The label must bear the following particulars: (a) the name or trade name and address of the manufacturer. For devices imported into the Community, in view of their distribution in the Community, the label, or the outer packaging, or instructions for use, shall contain in addition the name and address of either the person responsible referred to in Article 14 (2) or of the authorized representative of the manufacturer established within the Community or of the importer established within the Community, as appropriate; (b) the details strictly necessary for the user to identify the device and the contents of the packaging; (c) where appropriate, the work 'STERILE'; (d) where appropriate, the batch code, preceded by the word 'LOT', or the serial number; (e) where appropriate, an indication of the date by which the device should be used, in safety, expressed as the year and month (f) where appropriate, an indication that the device is for single use; (g) if the device is custom-made, the words 'custom-made device'; (h) if the device is intended for clinical investigations, the words 'exclusively for clinical investigations'; (i) any special storage and/or handling conditions; (j) any special operating instructions; (k) any warnings and/or precautions to take;	Use harmonized standards to gain presumption of compliance wherever possible.
(l) year of manufacture for active devices other than those covered by (e). This indication may be included in the batch or serial number; (m) where applicable, method of sterilization.	Use harmonized standards to gain presumption of compliance wherever possible.

Essential Requirement	Guidance
13.4 If the intended purpose of the device is not obvious to the user, the manufacturer must clearly state it on the label and in the instruction leaflet.	Use harmonized standards to gain presumption of compliance wherever possible.
13.5 Where reasonable and practicable, the devices and detachable components must be identified, wherever appropriate in terms of batches, to allow all appropriate action to detect any potential risk posed by the devices and detachable components.	Use harmonized standards to gain presumption of compliance wherever possible.
13.6 Where appropriate, the instructions for use must contain the following particulars: (a) the details referred to in Section 13.3, with the exception of (d) and (e); (b) the performances referred to in Section 3 and any undesirable side-effects; (c) if the device must be installed with or connected to other medical devices or equipment in order to operate as required for its intended purpose, sufficient details of its characteristics to identify the correct devices or equipment to use in order to obtain a safe combination; (d) all the information needed to verify whether the device is properly installed and can operate correctly and safely, plus details of the nature and frequency of the maintenance and calibration needed to ensure that the devices operate properly and safely at all times; (e) where appropriate, information to avoid certain risks in connection with implantation of the device; (f) information regarding the risks of reciprocal interference posed by the presence of the device during specific investigations or treatment; (g) the necessary instructions in the event of damage to the sterile packaging and, where appropriate, details of appropriate methods of re-sterilization;	Use harmonized standards to gain presumption of compliance wherever possible. This means the manufacturer must be able to prove compliance by testing, preferably independent testing.
(h) if the device is reusable, information on the appropriate processes to allow reuse, including cleaning, disinfection, packaging and, where appropriate, the method of sterilization of the device to be re-sterilized, and any restriction on the number of reuses. Where devices are supplied with the intention that they be sterilized before use, the instructions for cleaning and sterilization must be such that, if correctly followed, the device will still comply with requirements in Section 1;	Use harmonized standards to gain presumption of compliance wherever possible. This means the manufacturer must be able to prove compliance by testing, preferably independent testing.

Essential Requirement	Guidance
(i) details of any further treatment or handling needed before the device can be used (for example, sterilization, final assembly, etc.); (j) in the case of devices emitting radiation for medical purposes, details of the nature, type, intensity and distribution of this radiation. The instructions for use must also include details allowing the medical staff to brief the patient on any contra-indications and any precautions to be taken. These details should cover in particular: (k) precautions to be taken in the event of changes in the performance of the device; (l) precautions to be taken as regards exposure, in reasonably foreseeable environmental conditions, to magnetic fields, external electrical influences, electrostatic discharge, pressure or variations in pressure, acceleration, thermal ignition sources, etc.; (m) adequate information regarding the medicinal products which the device in question is designed to administer, including any limitations in the choice of substances to be delivered; (n) precautions to be taken against any special, unusual risks related to the disposal of the device; (o) medicinal substances incorporated into the device as an integral part in accordance with Section 7.4; (p) degree of accuracy claimed for devices with a measuring function;	Use harmonized standards to gain presumption of compliance wherever possible. This means the manufacturer must be able to prove compliance by testing, preferably independent testing.
14. Where conformity with the essential requirements must be based on clinical data, as in Section I (6), such data must be established in accordance with Annex X.	This should not be taken to imply that clinical evaluation of the device will necessarily be required. MHRA and other European regulators are demanding more clinical data and often a review of the literature on its own will be considered inadequate, especially for higher risk devices. Use of harmonized standards for clinical evaluation are: EN 14155-1: 2003 Clinical investigation of medical devices for human subjects – Part 1: General requirements; and EN 14155-2: 2003 Clinical investigation of medical devices for human subjects – Part 2: Clinical investigation plans. These replaced EN 540: 1993 Clinical investigation of medical devices for human subjects.

Appendix 5: List of Important Documents and Standards

- Council Directive 93/42/EEC of 14 June 1993 concerning medical devices (MDD).
- Council Directive 90/385/EEC of 20 June 1990 concerning active implantable medical devices (AIMD).
- Council Directive 98/79/EC of 27 October 1998 concerning in vitro diagnostic medical devices (IVD MDD).
- Council Directive 2000/70/EC of 16 November 2000 concerning human blood or plasma (Human Blood Directive).
- Commission Directive 2003/12/EC of 3 February 2003 on the reclassification of breast implants in the framework of Directive 93/42/EEC concerning medical devices (Breast Implant Reclassification Directive).
- Commission Directive 2003/32/EC of 23 April 2003 introducing detailed specifications as regards the requirements laid down in Council Directive 93/42/EEC with respect to medical devices manufactured utilizing tissues of animal origin (Animal Tissues Directive).
- Guide to the Implementation of Directives Based on New Approach and Global Approach (European Commission).
- List of European Harmonized Standards (Official Journal of the European Communities).
- Health Canada's policy on the use of recognized standards.
- ISO 9001: 1994 Quality Systems - Model for Quality Assurance in Design, Development, Production, Installation and Servicing.
- ISO 9001: 2000: Quality Management System Requirements.
- FDA's Quality System Regulation, Part 820 of 21 CFR (US Code of Federal Regulations).
- FDA's CDRH web site and all guidance, especially that provided by Device Advice.
- Canadian Medical Devices Regulations (1998) and subsequent amendments.
- ISO 13485: 1996 Quality Systems - Medical Devices - Particular requirements for the application of ISO 9001.
- ISO 14969: 1999 Quality system - Medical devices - Guidance on the application of ISO 13485 and ISO 13488.
- ISO 13485: 2003 Medical devices - Quality management systems - Requirements for regulatory purposes.
- PD ISO/TR 14969: 2004 Medical devices - Quality management systems - Guidance on the application of ISO 13485: 2003.
- EN 12442-1:2000 Animal tissues and their derivatives utilized in the manufacture of medical devices. Analysis and management of risk.
- ISO 14971:2000: Medical devices – Application of risk management to medical devices.
- EN 12442-2:2000 Animal tissues and their derivatives utilized in the manufacture of medical devices. Controls on sourcing, collection and handling.
- EN 12442-3:2000 Animal tissues and their derivatives utilized in the manufacture of medical devices. Validation of the elimination and/or inactivation of viruses and transmissible agents.

- Global Harmonization Task Force, various documents please see www.ghtf.org.
- Various guidance documents on the application of the Canadian Devices Regulations, please visit the Health Canada website at: http://www.hc-sc.gc.ca/dhp-mps/md-im/applic-demande/guide-ld/index_e.html

UK MHRA Useful Guidance Documents

The main site can be accessed via www.mhra.gov.uk but "Devices information" takes you effectively to the old MDA site: http://devices.mhra.gov.uk [www.medical-devices.gov.uk takes you to the same location]. Clicking on 'Publications' and then 'Regulatory' leads to the 'Regulatory Publications' section where the most useful documents (pdfs) can be found.

Guidance on The EC Medical Devices Directives at the MHRA web site includes (but is not limited to) the following:

Guidance Notes for Manufacturers on Clinical Investigations to be carried out in the UK [direct1]

- Form PCA 1 [form-PCA1]
- Form PCA 2 [form-PCA2]

Information for Clinical Investigators [direct3]

Pre-clinical Assessment: Guidance for Assessors [direct4]

Guidance on Biocompatibility Assessment [direct5]

Guidance Notes for Manufacturers of Class 1 Medical Devices [direct7]

Guidance Notes for the Registration of Persons Responsible for Placing Devices on the Market [direct8]; [append-ab] & [formrg2]

Guidance Notes for Manufacturers on Statistical Considerations for Clinical Investigations of Medical Devices [direct17]

Guidance Notes for the Registration of Person Responsible for Placing *In-Vitro* Diagnostic Medical Devices on the Market [direct18]; [form-rg3]

Guidance Notes on In Vitro Diagnostic Medical Devices Directive 98/79/EC [direct19]

Directives Bulletins

The CE Marking [bull2]

The Vigilance System [bull3]

Conformity Assessment Procedures **Updated: February 2004** [bull4]

The Notified Body [bull6]

Information about the EC Medical Devices Directives [bull8]

The Classification Rules [bull10]

Sale and Supply of In Vitro Diagnostic Medical Devices (IVDs) [bull1]

Standards [bull13]

Medical Devices and Medicinal Products [bull17]

(Previously 18A) The Medical Devices Regulations: Implications on Healthcare and other Related Establishments [bull18]

Own Brand Labeling and Rented Products [bull19]

Conformity Assessment Procedures under the In Vitro Diagnostic Medical Devices Directive 98/79/EC **Updated: February 2004** [bull20]

Application for the Exceptional use of non-complying devices [Humanitarian Bulletin]

Other MDA Publications:

Enforcement Policy - Compliance Inspections and Action - Your Rights

Post-market Surveillance of CE Marked Joint Replacement Implants including Guidance to Manufacturers on Post-Market Clinical Studies [pms]

Guidance on the Medical Devices vigilance system for CE marked joint replacement implants [era-joint.pdf]

Guidance on the Medical Devices vigilance system for CE marked artificial heart valves [era-heart]

Guidance on the Medical Devices vigilance system for CE marked artificial breast implants [era-breast]

Guidance on the Medical Devices vigilance system for CE marked artificial coronary stents [coronarystents]

Optical Flyer – The Application of the EC Medical Devices Directive to Ophthalmic Medical Practitioners, Optometrists, Dispensing Opticians and Manufacturing Opticians [opt-regs]

Guidance Notes for Manufacturers of Custom-made Devices [direct9]

Guidance Notes for Manufacturers of Dental Appliances (Custom Made Devices) [direct10]

Guidance Notes for Manufacturers of Prosthetic and Orthotic Appliances [direct16]

Guidance on the Recall of Medical Devices [guidance]

Changes to the Registration of Medical Devices

http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&useSecondary=true&ssDocName=CON007535&ssTargetNodeId=578

Clinical Investigation - Medical Devices Fees Regulations:

http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&useSecondary=true&ssDocName=CON007537&ssTargetNodeId=578

MDA Safety Warnings:

http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodeId=363

Appendix 6: Comparison Chart of ISO 13485:1996, ISO 13485:2003 and FDA's QSR

The table below lists the corresponding clauses of ISO 13485:1996, ISO 13485:2003, and the Quality System Regulation, respectively.

ISO 13485:1996	ISO 13485:2003	FDA Quality System Regulation
1. Scope	1. Scope	820.1 Scope 820.1 (a) Application
4.1 Management Responsibility 4.1.1 Quality Policy 4.1.2 Organization/Resources 4.1.3 Management Review	5.1 Management Commitment 5.3 Quality Policy 5.4.1 Quality Objectives 5.5.1 Responsibility and Authority 6.1 Provision of Resources 6.2.1 Human Resources 5.5.2 Customer Focus 5.6.1 Management Review 8.5.1 Improvement	820.20 Management Responsibility 820.20 (a) Quality policy 820.20 (b) Organization 820.20 (c) Management Review 820.25 (a) General
4.2 Quality System 4.2.1 General 4.2.2 Quality System Procedures 4.2.3 Quality Planning	4.1 QMS General Requirements 4.2.2 Quality Manual 4.2.1 Documentation Requirements General 5.4.2 Quality management System Planning 7.1 Planning of Product Realization	820.5 Quality System 820.20 (b) Organization 820.20 (d) Quality Planning 820.20 (e) Quality System Procedures 820.30 (h) Design Transfer 820.181 Device Master Record 820.186 Quality System Record
4.3 Contract Review	5.2 Customer Focus 7.2.1 Determination of Requirements Related to Product 7.2.2 Review of Requirements Related to Product 7.2.3 Customer Communication	820.50 (b) Purchasing Data 820.160 (b) Distribution Records
4 Design Control 4.4.1 General 4.4.2 Design Development and Planning 4.4.3 Organizational and Technical Interfaces	7.3 Design and Development 7.3.1 Design and Development Planning	820.30 Design Controls 820.30 (a) General 820.30 (b) Design & Development Planning 820.30 (h) Design Transfer
4.4.4 Design Input	7.2.1 Determination of Requirements Related to	820.30 (c) Design Input

ISO 13485:1996	ISO 13485:2003	FDA Quality System Regulation
	Product 7.3.2 Design & Development Inputs	
4.4.5 Design Output	7.3.3 Design & Development Outputs	820.30 (d) Design Output
4.4.6 Design Review	7.3.4 Design & Development Review	820.30 (e) Design Review
4.4.7 Design Verification	7.3.5 Design & Development Verification	820.30 (f) Design Verification
4.4.8 Design Validation	7.3.6 Design & Development Validation	820.30 (g) Design Validation 820.70 (i) Automated Processes
4.4.9 Design Changes	7.3.7 Control of Design & Development Changes	820.30 (i) Design Changes 820.70 (b) Production & Process Changes
4.5 Document and Data Control 4.5.1 General 4.5.2 Document and Data Approval and Issue 4.5.3 Document and Data Changes	4.2.3 Control of Documents	820.40 Document Control 820.40 (a) Document Approval & Distribution 820.40 (b) Document Changes 820.180 General 820.180 (a) Confidentiality
4.6 Purchasing 4.6.1 General 4.6.2 Evaluation of Subcontractors	7.4.1 Purchasing Process	820.50 Purchasing Controls 820.50 (a) Evaluation of Suppliers, Contractors & Consultants
4.6.3 Purchasing Data 4.6.4 Verification of Purchased Product 4.6.4.1 Supplier Verification at Subcontractor's Premises 4.6.4.2 Customer Verification of Subcontractor Product	7.4.2 Purchasing Information 7.4.3 Verification of Purchased Product	820.50 (b) Purchasing Data 820.80 (a) General
4.7 Control of Customer-Supplied Product	7.5.4 Customer Property	820.80 (a) General
4.8 Product Identification and Traceability	7.5.3 Identification & Traceability	820.60 Identification 820.65 Traceability
4.9 Process Control	6.3 Infrastructure 6.4 Work Environment 7.5.1 Control of Production & Service Provision 7.5.2 Validation of Processes for Production and Service Provisions	820.70 (a) Production & Process Controls -- General 820.70 (e) Environmental Control 820.70 (d) Personnel 820.70 (e) Contamination Control 820.70 (f) Buildings 820.70 (g) Equipment 820.70 (h) Manufacturing Material 820.75 (a) (b) (c) Process

ISO 13485:1996	ISO 13485:2003	FDA Quality System Regulation
		validation 820.170 (b) Installation
4.10 Inspection and Testing 4.10.1 General	7.1 Planning of Product Realization 8.1 Measurement , Analysis & Improvement	820.80 (a) Receiving, In-process & Finished Device Acceptance – General
4.10.2 Receiving Inspection and Testing	7.4.3 Verification of Purchased Product	820.80 (b) Receiving Acceptance Activities
4.10.3 In-process Inspection and Testing	8.2.4 Monitoring & Measurement of Product	820.80 (c) In-process Acceptance Activities
4.10.4 Final Inspection and Testing	8.2.4 Monitoring & Measurement of Product	820.80 (d) Final Acceptance Activities
4.10.5 Inspection and Test Records	7.5.3 Identification & Traceability	820.80 (e) Acceptance Records
4.11 Inspection, Measuring and Test Equipment 4.11.1 General 4.11.2 Control Procedure	7.6 Control of Monitoring & Measuring Devices	820.70 (c) Environmental Control 820.71 Inspection, Measuring & Test Equipment 820.72 (a) Control of Inspection, Measuring & Test Equipment 820.72 (b) Calibration 820.72 (b) (1) Calibration Standards 820.72 (b) (2) Calibration Records
4.12 Inspection and Test Status	7.5.3 Identification & Traceability	820.86 Acceptance Status
4.13 Control of Nonconforming Products 4.13.1 General	8.3 Control of Non-conforming Product	820.90 Nonconforming Product 820.90 (a) Control of Nonconforming Product
4.13.2 Review and Disposition of Nonconforming Product	8.3 Control of Non-conforming Product	820.90 (b) Nonconforming Review & Disposition
4.14 Corrective and Preventive Action 4.14.1 General 4.14.2 Corrective Action	8.5.2 Corrective Action	820.100 Corrective & Preventive Action 820.100 (a) Procedures for Implementing Corrective & Preventive Action 820.100 (b) Documentation of All Related Activities 820.198 Complaint Files
4.14.3 Preventive Action	8.5.3 Preventive Action	820.100 Corrective & Preventive Action 820.100 (a) Procedures for Implementing Corrective & Preventive Action 820.100 (b) Documentation of All

ISO 13485:1996	ISO 13485:2003	FDA Quality System Regulation
		Related Activities 820.198 Complaint Files
4.15 Handling, Storage, Packaging, Preservation and Delivery 4.15.1 General 4.15.2 Handling	6.4 Work Environment 7.5.1 Control of Production & Service Provision	820.120 Device Labeling 820.130 Device Packaging 820.140 Handling
4.15.3 Storage	7.5.5 Preservation of Product	820.150 Storage
4.15.4 Packaging	7.5.5 Preservation of Product	820.130 Device Packaging
4.15.5 Preservation	7.5.5 Preservation of Product	820.130 Device Packaging
4.15.6 Delivery	7.5.5 Preservation of Product	820.160 (a) Distribution Control for Finished Products
4.16 Control of Quality Records	4.2.4 Control of Records	820.30 (j) Design History File 820.180 General Requirements 820.180 (a) Confidentiality 820.180 (b) Record Retention Period 820.180 (c) Exceptions 820.181 Device Master Record 820.184 Device History Record 820.186 Quality System Record
4.17 Internal Quality Audits	8.2.2 Internal Audit 8.2.3 Monitoring & Measurement of Processes	820.22 Quality Audit
4.18 Training	6.2.2 Competence, Awareness & Training	820.25 (b) Training
4.19 Servicing	7.5.1 Control of Production & Service Provision	820.200 Servicing
4.20 Statistical Techniques 4.20.1 Identification of Need 4.20.2 Procedures	8.1 Measurement, Analysis & Improvement 8.2.3 Monitoring & Measurement of Processes 8.2.4 Monitoring & Measurement of Product 8.4 Analysis of Data	820.250 Statistical Techniques

Appendix 7: Canadian Firms and the Small Business Discount for the Review of Medical Devices under the Medical Device User-Fee and Modernization Act of 2002 (MDUFMA)

Under MDUFMA, the U.S. Food and Drug Administration can charge a fee for the review of medical devices. There is a provision within MDFMA that allows for a reduction in fees for small businesses. To qualify for reduced fees, a small business must submit U.S. Federal income tax forms (for itself, and all affiliates, partners, and parent firms), showing that its sales and receipts do not exceed $30 million.

A Canadian firm may meet the requirement by submitting an 1120- F (U.S. Income Tax return of a Foreign Corporation) along with Form 8833 (treaty-based return under Section 6114) to obtain the small business reduced fee for premarket reviews. These forms must be completed and submitted to the United States Internal Revenue Service (IRS). Upon completion of the IRS review, the forms may be submitted to FDA to be used to determine the firm's eligibility for reduced fees.

The Canadian firm is often exempt from taxation in the U.S. Under the U.S. – Canada Tax Treaty, Canadian firms are exempt from U.S. taxes providing they do not have an establishment within the United States. Article VII (1) of the Tax Treaty states that, "The business profits of a resident of a Contracting State shall be taxable only in that State unless the resident carries on business in the other Contracting State through a permanent establishment situated therein. If the resident carries on, or has carried on, business as aforesaid, the business profits of the resident may be taxed in the other State but only so much of them as is attributable to that permanent establishment."

In addition, a U.S. subsidiary of a Canadian parent firm may itself qualify as a "small business" for the purpose of receiving a reduction in user fees even if the parent firm does not file a U.S. tax return, provided that the Canadian parent firm is identified on the corresponding schedule of the subsidiary's U.S. tax return and their combined income is under the $30 million threshold for qualification. In this instance the FDA will grant only one first *free* PMA to the first filer, whether the Canadian parent or U.S. subsidiary; however, all other reductions in fees will continue to apply.

Several Canadian firms have used this mechanism to obtain a reduced small business fee. Both FDA and the U.S. Department of Commerce are routinely advising all Canadian firms that contact them about this mechanism. Canadian Firms are encouraged to contact FDA for details. Please call DSMICA at 800-638-2041 or email us at DSMICA@CDRH.FDA.GOV for further assistance.

Glossary of Terms Used in the Field of Medical Device Regulation

Canadian Medical Devices Regulations (CMDRs)
Regulations governing the sale and advertising for sale of medical devices in Canada.

Competent Authority
The body appointed by each national government within the EU to enforce compliance with the MDD in that country.

Conformity Assessment Bodies
Registrars and notified bodies recognized under Mutual Recognition Agreements as having the authority to perform assessments of manufacturer's compliance against the requirements of a jurisdiction in which that registrar or notified body is not established.

Conformity Assessment Procedure
A route by which a manufacturer may demonstrate compliance with the MDD, to obtain the CE Marking, as described in Article II and Annexes II to VIII of the MDD.

CE Marking
The mark that may be applied to a product to demonstrate that it conforms to the requirements of a European Directive. The CE marking must be applied to all medical devices sold within the EU to demonstrate that the device conforms to the essential requirements of the MDD.

CFR
US Code of Federal Regulations.

Controlled Documents
All internally generated documents that have been designated as pertaining to the operation of its quality management system. These include all: policies, procedures, work instructions, records, job descriptions, and organizational charts.
Externally generated documents that have been designated as impacting upon the operation of its quality management system or affecting product quality. These include: relevant ISO, EN, ANSI and other standards, relevant medical devices regulations, and client–supplied product specifications, drawings, and instructions.

Declaration of Conformity
A formal statement by a manufacturer that a product complies with the relevant essential requirements of the MDD.

Design Dossier
A description of the design, manufacture, and performance of a product. It must include all the documentation needed to assess whether the product conforms to the applicable essential requirements of the MDD.

Design History File (DHF)
FDA term for a compilation of records that describes the design history of a finished device.

Device Master Record (DMR)
FDA term for a compilation of records containing the procedures and specifications for a finished device.

Device History Record (DHR)
FDA term for a compilation of records containing the production history of a finished device.

Directive
European legislation published in the Official Journal of the European Communities. European Directives have no force in law until they have been enacted through member-state legislation.

Essential Requirements
A list of requirements contained within the MDD (Annex I) that, if applicable, must be addressed and documented before the CE marking can be applied to a medical device.

FDA
The US Food and Drug Administration: the authority that regulates the manufacture of food, drugs, biologics and devices in the US.

Federal Food, Drug and Cosmetic Act (FD&C Act)
One of the major laws that gives the FDA its regulatory authority.

Finished Device
The FDA Quality System Regulation defines a finished device as any device or accessory to any device that is suitable for use or capable of functioning, whether or not it is packaged, labeled or sterilized.

GMP
The FDA Good Manufacturing Practice (GMP) Regulation governing the quality system requirements for products regulated under the FDA. The GMP pertaining to medical devices is set out in the Quality System Regulation, Part 820 of 21 CFR.

Harmonized Standard
In Europe -- A technical specification (European Standard or harmonized document) adopted by the European Commission through CEN (European Committee for Standardization) and published in the Commission's Official Journal.

In Canada -- Health Canada has developed a policy on the use of recognized standards in establishing the safety and effectiveness of medical devices. This policy can be found on the Health Canada website at the following address:

http://www.hc-sc.gc.ca/dhp-mps/md-im/applic-demande/guide-ld/index_e.html

Health Canada

The organization that regulates medical devices in Canada, under the authority of the Canadian Food and Drugs Act.

Human Blood Directive

European Council Directive 2000/70/EC of 16 November 2000 concerning medical devices incorporating stable derivatives of human blood or human plasma.

Intended purpose (MDD definition)

The use for which the device is intended according to the data supplied by the manufacturer on the labeling, in the instructions for use/or in promotional material.

ISO 9000:2000

The International Organization for Standardization models for quality assurance. ISO 900:2000 is the model for design, development, production, and installation and servicing.

ISO 13485:1996 and ISO 13488:1996 Standards

The International Organization for Standardization's particular requirements for suppliers of medical devices that is more specific than ISO 9001 and ISO 9002, respectively. ISO 13485 represents a model for quality assurance in design, development, production, installation and servicing. ISO 13488 covers all of the foregoing except design. ISO 13485 and ISO 13488 should be applied in conjunction with the ISO 9001:1994 and ISO 9002:1994, respectively. These are not stand-alone standards. The European version of ISO 13485 and ISO 13488 is EN ISO 13485 and EN ISO 13488 respectively.

ISO 13485:2003

ISO 13485:2003 Medical devices – Quality management systems—Requirements for regulatory purposes replaces ISO 13485:1996 and ISO 13488:1996. This is a stand-alone standard, modeled on ISO 9001:2000, but does not require continual improvement or customer satisfaction.

IVDD

In Vitro diagnostic device.

IVD MDD

European Council Directive 98/79/EC of 27 October 1998 concerning in vitro diagnostic medical devices.

Mandatory Problem Reporting (CMDRs definition)

The Health Canada requirement that manufacturers and importers of devices make preliminary and final reports to Health Canada concerning any incident involving their device that:
(a) Is related to the failure or deterioration of the device or inadequacies in the labeling or directions for use; and
(b) Has led to a death or serious deterioration in the health of a patient, user or other person; or could have led to a death or serious deterioration in the health of a patient, user or other person.

Manufacturer (FDA definition)

Any person, who designs, manufactures, fabricates, assembles, or processes a finished device. Manufacturer includes but is not limited to those who perform the functions of contract sterilization, installation, re-labeling, re-manufacturing, re-packing, or specification development, and initial distributors of foreign entities performing these functions.

Manufacturer (MDD definition)

The natural or legal person with responsibility for the design, manufacture, packaging and labeling of a device before it is placed on the market under his own name, regardless of whether these operations are carried out by that person himself or on his behalf by a third party.

Manufacturer (CMDRs definition)

A person who sells the medical device under their own name, or under a trade-mark, design, trade name or other name or mark owned or controlled by the person, and who is responsible for designing, manufacturing, assembling, processing, labeling, packaging, refurbishing or modifying the device, or for assigning to it a purpose, whether those tasks are performed by that person or on their behalf.

MDD (Medical Device Directive)

The European Council Directive 93/42/EEC of 14 June 1993, concerning medical devices.

Medical Device (FDA definition)

An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, that is:

- Recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them;
- Intended for use in the diagnosis of diseases or other conditions, or in the cure, mitigation, treatment, or prevention of disease in man or other animals; or
- Intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its principal intended purposes.

Medical Device (MDD definition)

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 for human beings for the purpose of:

- Diagnosis, prevention, monitoring, treatment or alleviation of disease;
- Diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap; Investigation, replacement or modification of the anatomy or of a physiological process;
- Control of conception;

Which does not achieve its principle 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.

Medical Device (Canadian Food & Drugs Act and the CMDRs definition)

An article, instrument, apparatus or contrivance, including a component, part or accessory of one, that is manufactured, sold or represented for use in:

- The diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state, or its symptoms, in a human being;
- The restoration, correction or modification of a body function or the body structure of a human being;
- The diagnosis of pregnancy in a human being; or
- The care of a human being during pregnancy and at and after the birth of a child, including the care of the child.

It includes a contraceptive device but does not include a drug.

Medical Device Reports (MDRs)

Reports required by the FDA when manufacturers and distributors receive or become aware of information that reasonably suggests that a device they manufacture or distribute:

- Caused or contributed to a death, serious illness or serious injury; or
- Malfunctioned, and there is a probability that if the malfunction were to recur, the devices would cause or contribute to a death, serious injury or serious illness.

Medicines and Healthcare products Regulatory Agency (MHRA)

The UK Competent Authority for the MDD.

Notified Body

A body (usually a company) approved by the competent authority to assess manufacturers' compliance with the MDD in accordance with its provisions. Such bodies are 'notified' to the European Commission and as such may operate anywhere within the EU.

Postmarket Surveillance

A system established by the manufacturer to ensure that feedback from the marketplace provides early warning of quality problems. Postmarket surveillance is required by the EU, Canada and the US.

Premarket Approval

FDA approval to market a particular medical device. Premarket approval requirements apply to Class III devices only and are set out in Section 515 of the FD&C Act.

Premarket Notification (510(k))

A manufacturer's submission to the FDA containing information to show that a medical device is substantially equivalent to a legally marketed device.

Registrar

A third party auditor who assesses a firm's quality system. A registrar is accredited by a national body, such as the Standards Council of Canada, the Registrar Accreditation Board (US) or the UK National Accreditation Council for Certified Bodies.

Safe Medical Devices Act

A US law, enacted in 1990, which broadens the FDA's authority to regulate medical devices.

Safety and Effectiveness Requirements

Specific safety and effectiveness requirements pertaining to the design and manufacture of medical devices intended to ensure that the health or safety of patients, users or others is not adversely affected. Health Canada stipulates safety and effectiveness requirements for medical devices that are similar to the MDD's essential requirements.

Technical Documentation (MDD)

Information on each product relating to: classification, description, intended use— including use with other devices, performance characteristics, evidence that all safety and effectiveness requirements for the various regulatory jurisdictions have been satisfied, harmonized standards used, key documents that demonstrate product conformance, risk analysis, clinical data, quality system approval, product approvals and all associated documents.

Vigilance Reporting

A requirement under the MDD, whereby member states must ensure that any reports of adverse incidents involving medical devices in the marketplace are recorded and evaluated centrally. Manufacturers must put in place procedures to respond to such reports, by evaluating the causes, reporting findings to competent authorities and taking the necessary corrective action.