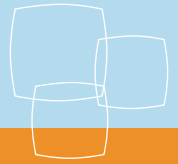




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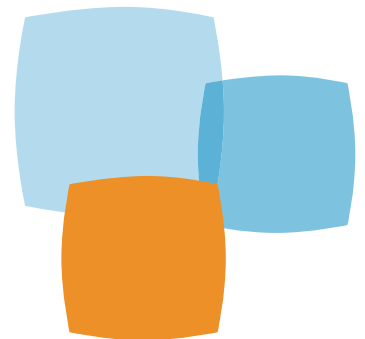
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Canada



Quality System Requirements for Medical Devices

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

2010 Version



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Aussi offert 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 2010*. Une version électronique du document français est disponible à l'adresse suivante : <http://www.ic.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 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 27 April 1998. Revised versions were published in 2001 and 2005 as significant changes had occurred in many areas. Changes continue as the industry moves ever closer towards global harmonization of quality systems for medical devices, resulting in this updated 2010 guide.

The original guide proved to be extremely popular and Industry Canada and the Department of Foreign Affairs and International Trade have contracted *Orion Canada Inc.* to update it. This 2010 version addresses current requirements; it is recommended for those new to medical devices and to experienced practitioners.

The increasing use of ISO 13485: 2003 Medical devices - Quality management systems - Requirements for regulatory purposes, as the world standard, is important to understand. This standard is complemented by PD ISO/TR 14969: 2004 Medical devices - Quality management systems - Guidance on the application of ISO 13485: 2003.

This 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 including the revision 2007/47/EC and 98/79/EC of 27 October 1998, concerning in vitro diagnostic medical devices; Commission Directives 2000/70/EC of 16 November 2000, concerning Human Blood or Plasma; 2003/12/EC, 3 February 2003, on the reclassification of breast implants 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, including device classification, registering a quality system, selecting a registrar or notified body, post-market surveillance and problem reporting, labeling, EU representation, and the Federal Drug Administration's (FDA) premarket notification and premarket approval.

Useful information sources pertaining to each jurisdiction are also identified in the reference guide.

Chapter 1: The European Union Requirements

Regulatory Framework

New Approach Directives and Revision

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 regulatory product and safety requirements of individual member states with “essential requirements” covering all Europe, namely European Community Directives (called New Approach Directives). The overview of the Directives was updated in the “New Approach and Global Approach.” The list of relevant directives can be found at

http://ec.europa.eu/enterprise/policies/single-market-goods/documents/list-directives3/index_en.htm

Also available at this location is a link to the “Blue Guide: The Guide to the Implementation of Directives Based on New Approach and Global Approach.”

http://ec.europa.eu/enterprise/policies/single-market-goods/documents/blue-guide/index_en.htm

It should be noted the New Approach has been revised. The aim of the revision is to reinforce the role and credibility of CE marking, so that remaining obstacles to the free movement of goods in a single market can be removed and trade increased. For more information, please see the “New Approach” at http://ec.europa.eu/enterprise/policies/single-market-goods/regulatory-policies-common-rules-for-products/new-approach/index_en.htm

More details are available at the “New Legislative Framework”:

http://ec.europa.eu/enterprise/policies/single-market-goods/regulatory-policies-common-rules-for-products/new-legislative-framework/index_en.htm

The changes in the New Approach move the way other directives are regulated closer to the way that medical devices are treated, and they require relatively few changes to company operations to account for them.

There were two important legal instruments that set the framework for the New Approach: 93/465/EEC: Council Decision of 22 July 1993, concerning the modules for the various phases, the conformity assessment procedures, and the rules for the affixing and use of the CE conformity marking that are intended to be used in the technical harmonization directives is available at

http://eurlex.europa.eu/smartapi/cgi/sga_doc?smartapi!celexapi!prod!CELEXnumdoc&lg=en&numdoc=31993D0465&model=guichett

Council Regulation (EEC) No 339/93 of 8 February 1993, on checks for conformity with the rules on product safety in the case of products imported from third countries is available at

<http://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31993R0339:EN:HTML>

Both of the above regulations were repealed on 23 June 2008, to enable the implementation of the New Approach Revision.

The key legal instruments are:

- Regulation (EC) No. 764/2008 of the European Parliament and the Council of 9 July 2008, laying down procedures relating to the application of certain national technical rules for products lawfully marketed in another Member State, and repealing Decision No. 3052/95/EC.
- Regulation (EC) No. 765/2008 of the European Parliament and the Council of 9 July 2008, setting out the requirements for accreditation and market surveillance relating to the marketing of products, and repealing Regulation (EEC) No. 339/93.
- Decision No. 768/2008/EC of the European Parliament and the Council of 9 July 2008 on a common framework for the marketing of products, and repealing Council Decision 93/465/EEC.

The Regulations are applicable from the 1 January 2010. The changes will be “...fed into existing Directives when they are revised.” This means, given that the Medical Device Directive 93/42/EEC (MDD) and Active Implantable Medical Devices Directive 90/385/EEC (AIMDD) have already been revised (2007-2010) that no significant changes will occur until the outcome of any further revisions or the forthcoming Recast is implemented. It should also be noted that the New Approach Revision is regarded as *lex specialis*, meaning it only applies where there are no specific requirements already addressing the same objectives, as of course there are for medical devices.

The effect of these changes to medical devices should become clearer once the Recast consultation has been concluded; this process was started in 2008 and put on hold so that manufacturers could absorb the revisions of the MDD, AIMDD and the New Approach Revision. The Recast consultation is likely to resume sometime in 2010. Given the overall support for the New Approach by the medical device industry, and that the New Approach Revision reaffirms the key principles of the New Approach, the changes are likely to be readily accommodated.

In the New Approach Revision:

- Compliance with the essential requirements remains central to the process.
- Use of voluntary harmonised standards, including the presumption of conformity to the essential requirements for their scope remains.
- Conformity assessment still has a modular approach that is essentially unchanged and largely consistent with that used for medical devices. The manufacturer still has some choice in which modules to use.
- The legal manufacturer draws up a Declaration of Conformity and affixes the CE marking to indicate compliance with the directives.

The quality system referred to in the New Approach Revision modules is ISO 9001; the medical directives use ISO 13485 based on ISO 9001 which is now well established in the medical device industry as the global standard.

Detailed wording and definitions vary between the texts of the New Approach Revision and the current medical device directives but have essentially the same meaning and intent. Defined economic operators include the manufacturer, the authorised representative, the importer and the distributor. The latter two are not included in the medical directives definitions. One conflict in approach is where the New Approach decision document requires the importer, or distributor, but not the authorised representative, to provide an address on the product, packaging or on information provided with the product, i.e. instructions for use. This is the opposite of what is required by medical device directives and is clearly an item that will be the subject of future discussions at the Commission.

All economic operators, including importers and distributors, have responsibilities under the New Approach Revision, namely under clause (19) of Decision No. 768/2008/EC. They “...should take the appropriate measures to ensure that they make available on the market only products which are in conformity with the applicable legislation.” This means the importer should check that items such as technical documentation have been created, the product is appropriately CE-marked, a signed declaration of conformity exists, the product has appropriate information supplied with it and that it is written in appropriate languages. There may be other directives or tests that need to be complied with, and importers will clearly need to be aware of what these are.

Decision No. 768/2008/EC includes a basic template of what a Declaration of Conformity should include and is useful. In the past, there has been a lot of variation on how these were written for medical devices and IVDs.

The New Approach Revision includes changes that affect conformity assessment bodies (CABs), better known as Notified Bodies (NBs), within the medical sector. These changes include how they are designated and how they go about their very important work of conformity assessment; this is a crucial part of the CE marking process but this is beyond the scope of this document.

New Approach Medical Device Directives

The European Commission's medical device regulatory page and related issues for medical devices can be found at

http://ec.europa.eu/consumers/sectors/medical-devices/regulatory-framework/index_en.htm

This page includes copies of the directives in the Community languages and should be bookmarked and used to keep well informed of changes and issues.

New Approach Directives with CE marking requirements have been written for more than 20 product groups. For medical devices the three main directives are:

- Council Directive 93/42/EEC of 14 June 1993, concerning medical devices (MDD) became mandatory on 14 June 1998.
- Council Directive 90/385/EEC of 20 June 1990, on the approximation of the laws of the Member States relating to active implantable medical devices (AIMDD). This was first published on 20 June 1990, and became mandatory on 31 December 1994.
- Directive 98/79/EC of the European Parliament and the Council of 27 October 1998, on in vitro diagnostic medical devices (IVDD) became mandatory on 7 December 2003.

The MDD, AIMDD and IVDD contain essential requirements concerning safety, health, environment and consumer protection, conformity assessment routes, requirements for clinical evaluation or performance evaluation, criteria of the designation of notified bodies and the CE marking of conformity symbol.

The AIMDD contains essential requirements (ERs) and other items pertaining to active implantable medical devices. The specific requirements are not covered by this report but the AIMDD has been subject to the same revision process as the MDD and is now even closer to the MDD than was previously reported.

The IVDD was amended by Regulation (EC) No. 1882/2003 of the European Parliament and the Council of 29 September 2003, that updated Article 6, Committee on Standards and Technical Regulation's procedure which does not affect ERs. It is incorporated into the consolidated version of the IVDD available from the Europa web site identified earlier.

Other directives that modify the MDD cover human blood and derivative products, a reclassification of breast implants, devices manufactured utilizing tissues of animal origin, and a reclassification of hip, knee and shoulder joint replacements:

- 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 (referred to here 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 (referred to here as the Breast Implant Reclassification Directive).
- Commission Directive 2003/32/EC of 23 April 2003, introducing detailed specifications on the requirements laid down in Council Directive 93/42/EEC with respect to medical devices manufactured utilizing tissues of animal origin (referred to here as the Animal Tissues Directive).
- Commission Directive 2005/50/EC of 11 August 2005, on the reclassification of hip, knee and shoulder joint replacements in the framework of Council Directive 93/42/EEC concerning medical devices (referred to here as the Replacement Joint Directive).

The Breast Implant Reclassification Directive and Replacement Joint Directive reclassify products within their scope from Class IIb to Class III.

Manufacturers of the products indicated above need to read the appropriate directives for a complete understanding of all the changes.

MDD Revisions

The Revision of Medical Devices Directives 2007/47/EC (MDD Revision) has kept the name on the QS certificate the same as it is now "... 93/42/EEC," but has the formal title of: Directive 2007/47/EC of the European Parliament and of the Council of 5 September 2007, amending Council Directive 90/385/EEC on the approximation of the laws of the Member States relating to active implantable medical devices, Council Directive 93/42/EEC concerning medical devices and Directive 98/8/EC concerning the placing of biocidal products on the market. It is available at http://ec.europa.eu/consumers/sectors/medical-devices/regulatory-framework/index_en.htm

The changes arising from the MDD Revision are discussed in each section of the report and will be mandatory throughout the European Union (EU) from 21 March 2010, in the EU and European Free Trade Association (ETFA) countries. The revision applies to all previously CE marked products.

The Medicines and Healthcare products Regulatory Agency (MHRA - www.mhra.gov.uk) is the United Kingdom's (UK) Competent Authority and all medical device work regarding placing devices on the UK market is regulated by it. Go to "How we regulate" and then select "Devices." It is important to examine the information available at this site, especially in regard to guidance documents, bulletins and clinical trials. It is written 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 focus of this chapter is on the MDD and IVDD as these cover the vast majority of medical devices, and the approach used under the MDD for Class III devices matches most of the

expectations that European regulators have for active implantable medical devices. Specifics related to active implantable medical devices can be referenced in the AIMDD 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 is complemented by ISO/TR 14969: 2004 Medical devices - Quality management systems - Guidance on the application of ISO 13485: 2003.

ISO 13485: 2003 is the harmonised quality system standard for medical device directives. Whilst its use is voluntary, it is recommended to all medical device manufacturers and is consistent with the application of Good Manufacturing Practice (GMP) as required by the United States (US) Food and Drug Administration (FDA). ISO/TR 14969: 2004 is not a harmonised standard but is a useful reference for those implementing an ISO 13485 compliant quality system. Please note EN for Euro Norm is often placed in front of a standard adopted by CEN or CENELEC to indicate this. A standard only becomes harmonized to a directive when published on the officially recognised list for the directive in the Official Journal of the European Union (OJEU).

The previous versions of this guide referred to a number of changes that had occurred. 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 ceased 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 that ISO 13485: 1996 Quality Systems – Medical devices – Particular requirements for the application of ISO 9001 is no longer in use in Europe and cannot be purchased from the major standards bodies. However, the majority of requirements in the 2000 and 2003 versions are very similar, although the changes have moved the standard to be in closer compliance with US FDA Quality System Requirements (QS requirements or QSR) provided that the system is rigorously implemented.

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

There is no direct equivalent to EN ISO 13488: 2001 (this replaced EN 46002). As with ISO 9001: 2000, the manufacturer had to actively justify opting out of design controls that are now

termed “product realization.” EN ISO 13485: 2003 does have two very helpful annexes that are considered particularly useful references for Canadian based companies:

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

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

- Annex A (informative) Terms used in certain regulatory administration to describe documents referenced in this Technical Report
- 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. ISO 13485 is also recognized, but any required system has to be equivalent to it or better. Even 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 and as it was developed with the full assistance of the Global Harmonization Task Force (GHTF, www.ghtf.org) which includes the USA and Canada, it makes sense to use it. Canada also uses ISO 13485:2003 as a recognized standard for QS and this is discussed in the next chapter. This Reference Guide recommends the use of ISO 13485: 2003.

Global Harmonization Task Force (GHTF)

All readers are strongly encouraged to use the free downloads of related documents on the main study groups produced by the highly experienced group of experts that make up the GHTF.

Study Group 1: *Pre-market Evaluation*

Study Group 2: *Post-Market Surveillance/Vigilance*

Study Group 3: *Quality Systems*

Study Group 4: *Auditing*

Study Group 5: *Clinical Safety/Performance*

GHTF promotes convergence of regulatory requirements; this includes pre-market submissions, including the pilot program identified as the STED initiative. This originated 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 in the Final Documents section on the GHTF web site.

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 on associated labeling. Medical devices 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 phases of the AIMDD, MDD and IVDD have all passed.

Please note the definitions in Article 1 of the medical directives indicate that:

- ‘placing on the market’ means the first making available, in return for payment or free of charge, of a device other than a device intended for clinical evaluation or performance evaluation with a view to distribution and/or use on the Community market, regardless of whether it is new or fully refurbished.
- ‘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. [This includes clinical evaluation or performance evaluation.]

The legal ‘manufacturer’ is the entity placing the device on the Community market and is responsible for ensuring the requirements of the directives are met in full.

Human Blood Directive

The Human Blood Directive (Directive 2000/70/EC) is effectively an amendment of the 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.” [EMEA is now known as the European Medicines Agency (EMA or EMEA), please see:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000235.jsp&jsenabled=true] Batch release certificates from a State or designated laboratory are a requirement of this directive. It became mandatory on 13 June 2002. The transitional period was for five years, i.e., until 13 June 2007; with a further two years until 13 June 2009, for devices to be put into service (as was also done for the IVDD). The MDD Revision has added more requirements concerning human blood derivatives and the involvement of notified bodies (NBs). Annex I, section 7.4 now states:

“Where a device incorporates, as an integral part, a human blood derivative, the notified body shall, having verified the usefulness of the substance as part of the medical device and taking into account the intended purpose of the device, seek a scientific opinion from the EMEA, acting particularly through its committee, on the quality and safety of the substance including the clinical benefit/risk profile of the incorporation of the human blood derivative into the device. When issuing its opinion, the EMEA shall take into account the manufacturing process and the data related to the usefulness of incorporation of the substance into the device as determined by the notified body.

Where changes are made to an ancillary substance incorporated in a device, in particular related to its manufacturing process, the notified body shall be informed of the changes and shall consult the relevant medicines competent authority (i.e. the one involved in the initial consultation), in order to confirm that the quality and safety of the ancillary substance are maintained. The competent authority shall take into account the data related to the usefulness of incorporation of the substance into the device as determined by the notified body, in order to ensure that the changes have no negative impact on the established benefit/risk profile of the addition of the substance in the medical device.

When the relevant medicines competent authority (i.e. the one involved in the initial consultation) has obtained information on the ancillary substance, which could have an impact on the established benefit/risk profile of the addition of the substance in the medical device, it shall provide the notified body with advice, whether this information has an impact on the established benefit/risk profile of the addition of the substance in the medical device or not. The notified body shall take the updated scientific opinion into account in reconsidering its assessment of the conformity assessment procedure.”

This process aims to determine the usefulness of the human blood derived product through consultation with the EMEA (European Medicines Agency - www.emea.europa.eu) undertaken by the NB involved in the product’s assessment. The opinion of the EMEA must be drawn up within 210 days after it receives valid documentation. The NB may not certificate the design of the product if EMEA scientific opinion is not favourable. Please see Annex II Full quality assurance system of the MDD section 4.

Animal Tissues Directive

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). Article 1 of this directive makes it clear that it specifies requirements for non-viable products:

“...in relation to risks of transmitting transmissible spongiform encephalopathies (TSE) under normal conditions of use to patients or others, via medical devices manufactured utilising animal tissue which is rendered non-viable or non-viable products derived from animal tissue.”

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 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 provides clear indications of what is expected.

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: 2007 Medical devices utilizing animal tissues and their derivatives. Application of risk management.
- EN 12442-2: 2007 Medical devices utilizing animal tissues and their derivatives. Controls on sourcing, collection and handling.
- EN 12442-3: 2007 Medical devices utilizing animal tissues and their derivatives. Validation of the elimination and/or inactivation of viruses and transmissible spongiform encephalopathy (TSE) agents.

Guidance is available: MEDDEV 2.11/1 REV. 2 (January 2008) Application of Council Directive 93/42/EEC taking into account Commission Directive 2003/32/EC for medical devices utilising tissues or derivatives originating from animals susceptible for TSE at http://ec.europa.eu/consumers/sectors/medical-devices/documents/guidelines/index_en.htm

The MDD Revision under Article 1 Section 5 indicates that the MDD does not apply to viable animal tissues:

“(f) transplants or tissues or cells of animal origin, unless a device is manufactured utilizing animal tissue which is rendered non-viable or non-viable products derived from animal tissue.”

The MDD Revision has only added one word to paragraph 8.2 of the ERs:

“Tissues of animal origin must originate from animals that have been 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 ► **M5** transmissible ◀ agents must be addressed by implementation of validated methods of elimination or viral inactivation in the course of the manufacturing process.”

The Competent Authority (CA) contact points for the Animal Tissues Directive can be found at http://ec.europa.eu/enterprise/sectors/medical-devices/files/bse_tse_en.pdf

Viable transplants, tissue or cells of animal origin and viable derivatives are not covered by this directive but are regulated under the Advanced Therapies requirements:

Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007, on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004 [‘ATMP regulation.’]

The ATMP regulation also applies to viable transplants, tissue or cells of human origin and viable derivatives. Such products can be incorporated or combined with devices in an ancillary manner, as can human blood products and their directives as already indicated.

Products subject to the ATMP regulations are beyond the scope of this guide and are regulated by those responsible for medicines.

Breast Implant Reclassification Directive

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 1 September 2003, were required to be reassessed as Class III 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 1 September 2003.

Replacement Joint Directive

The Replacement Joint Directive (2005/50/EC) required all affected products subject to Annex II Full quality system to be in compliance with the amendment by 1 September 2009, and to have a valid design certificate. Products CE marked via the type-examination route of Annex III prior to 1 September 2007, are required to complete a conformity assessment as a Class III device and have a valid design certificate by no later than 1 September 2010.

Other Directives to Consider

There are always other directives to consider besides the main medical directives and those indicated here are of a general nature. In each specific product application there are likely to be additional directives to consider that are not discussed here, especially those to establish the state of the art that regulators expect manufacturers to consider in the New Approach.

It is useful to examine the “Interpretative documents” that help with some important cases. They are available at

http://ec.europa.eu/consumers/sectors/medical-devices/documents/interpretative-documents/index_en.htm

These include:

- [Interpretation of the relation between the revised Directives 90/385/EEC and 93/42/EEC concerning \(active implantable\) medical devices and Directive 2006/42/EC on machinery](#) (21 August 2009)
- [Interpretation of the relation between the revised Directive 93/42/EEC concerning medical devices and Directive 89/686/EEC on personal protective equipment](#) (21 August 2009)
- [Interpretative document of the Commission's services implementation of directive 2007/47/EC amending directives 90/385/EEC, 93/42/EEC and 98/8/EC](#) (5 June 2009)
- [Interpretation of the Medical Devices Directives in relation to medical device own brand labelers](#) (4 February 2008)

Guidance is provided at the ‘Borderline and classification issues’ web page:

http://ec.europa.eu/consumers/sectors/medical-devices/documents/borderline/index_en.htm

This includes the Manual on Borderline and Classification in the Community Regulatory Framework for Medical Devices Version 1.4 (05-2009).

PPE Directive

<http://ec.europa.eu/enterprise/sectors/mechanical/personal-protective-equipment/>

Some products used in medical facilities can be used for protective purposes, for medically intended purposes or sometimes for both, such as masks, goggles and gloves. The MDD Revision states in Article 1 paragraph 6:

“Where a device is intended by the manufacturer to be used in accordance with both the provisions on personal protective equipment in Council Directive 89/686/EEC (1) and this Directive, the relevant basic health and safety requirements of Directive 89/686/EEC shall also be fulfilled.”

Council Directive

The Council Directive 89/686/EEC of 21 December 1989, on the approximation of the laws of the Member States relating to personal protective equipment is often referred to as the PPE Directive.

The interpretative document of 21 August 2009, indicated above makes it clear “...that products which, according to the intention of its manufacturer, are to be used as a medical device and as a PPE at the same time must fulfil the relevant essential requirements of both directives.” The term ‘relevant’ is used “since only certain requirements of the PPE Directive are applicable while others are not.” The detailed requirements need to be assessed on a case-by-case basis.

Machinery Directive

<http://ec.europa.eu/enterprise/sectors/mechanical/machinery/>

The MDD Revision indicates that the MDD can overlap with Directive 2006/42/EC of the European Parliament and the Council of 17 May 2006, on machinery (the ‘Machinery Directive’), and that relevant hazards must be taken into account. The relevant basic health and safety requirements of the Machinery Directive in Annex I, which are more specific than those of Annex I of the MDD, must be complied with. A machine is defined as a powered mechanism with moving parts. In practice, this will not require a lot of extra requirements to be fulfilled and these are typically items of control and safety that the risk analysis will readily identify.

Environmental Directives

There has been a substantial increase in the introduction and application of environmental legislation in Europe in recent years, and some established directives have been or are being revised. It is important for manufacturers to review the environmental requirements. This section is intended to provide an initial insight to the key areas. It is recommended that manufacturers regularly visit the Europa web site to check on current legislation policy at http://ec.europa.eu/environment/policy_en.htm and, specifically concerning waste management, <http://ec.europa.eu/environment/waste/index.htm>, this site provides a lot of useful information.

Packaging & Packaging Waste (PPW) Directive (P&PWD)

European Parliament and Council Directive 94/62/EC of 20 December 1994, on Packaging and Packing Waste (PPW) is a directive with which all manufacturers, including medical device manufacturers, placing product on the market in the EU must comply.

The key requirements are to minimise packaging, consistent with application demands and to ensure the maximum reuse or recyclability. There is a need to show compliance with the essential requirements for the packaging produced for all products.

EuP Directive

The Directive 2005/32/EC of the European Parliament and of the Council of 6 July 2005 establishing a framework for the setting of ecodesign requirements for energy-using products and amending Council Directive 92/42/EEC and Directives 96/57/EC and 2000/55/EC of the European Parliament and of the Council (EuP Directive) does apply to medical devices.

It encourages all manufacturers of energy using products to adopt the principles of efficient energy use and environmental sustainability. It came into force in August 2007.

It is worth noting that representatives of the European trade association of the large European manufacturers COCIR (www.cocir.org) and the Commission have discussed the possibility of harmonising, under the EuP Directive, the international standard: EN IEC 60601-1-9:2008 Medical electrical equipment. General requirements for basic safety and essential performance. Collateral standard. Requirements for environmentally conscious design.

Batteries Directive

The Batteries and Accumulators and Waste Batteries and Accumulators 2006/66/EC (Batteries Directive) replaced the Batteries and Accumulators Containing Certain Dangerous Substances, Directive 91/157/EEC.

Batteries must be easy to remove and recycle. However portable medical equipment is exempt from the 0.002% prohibition on cadmium by weight use.

The Batteries Directive is primarily aimed at battery manufacturers and the materials used in production but this directive does affect those placing product on the market with batteries included. Medical device manufacturers may have to register as producers and keep records of the batteries placed on the market for the first time in their products and be responsible for financing the recovery of them.

Waste Electrical and Electronic Equipment (WEEE) Directive

All medical device manufacturers of electro-mechanical products should be working to Directive 2002/96/EC of the European Parliament and of the Council of 27 January 2003, on waste electrical and electronic equipment (WEEE) - Joint declaration of the European Parliament, the Council and the Commission relating to Article 9.

This requires all electrical and electronic products to be as recyclable as possible and for waste to be appropriately managed. There are labelling requirements including the use of the crossed-through wheelie bin symbol [as per EN 50419: 2006 Marking of electrical and electronic equipment in accordance with article 11(2) of Directive 2002/96/EC (WEEE)] indicating that the product should not enter the normal waste stream. There are amendments and secondary legislation on this topic, including proposed revisions that are available via the Europa web site at: http://ec.europa.eu/environment/waste/weee/index_en.htm. These include proposals, updates, and secondary legislation for both the WEEE and RoHS Directive (see next section).

The WEEE Directive does not apply to “implanted and infected medical devices.”

The proposed Recast of the WEEE Directive sets increased collection, reuse, recovery and recycling targets. All manufacturers need to design products for maximum recyclability and reuse of components.

The collection target for 2016 is 65% of the average weight of EEE placed on the national market during the two preceding years. Recovery and recycling targets are introduced for electro-medical devices of 75% for recovery and 55% for reuse and recycling. The Recast aims to harmonise the many different national registration and reporting requirements that should ultimately make this easier to implement.

There are financial implications for WEEE in the recast and registration requirements that help to enable cross-border information exchange and related transfer of money related to intra-Community transfer of products and waste. These financial implications will most likely be the responsibility of the producer or importer that first places product on the EU market. Costs incurred for the collection, treatment and disposal of WEEE will be recoverable from product sales and producers will be allowed to impose a “visible fee.”

The legislative procedure for both the recast of the WEEE and RoHS Directives will probably take around two years to complete and will be the subject of much debate.

RoHS Directive

Directive 2002/95/EC of the European Parliament and of the Council of 27 January 2003, on the restriction of the use of certain hazardous substances in electrical and electronic equipment, and Commission Decision of 18 August 2005, amending Directive 2002/95/EC of the European Parliament and of the Council for the purpose of establishing the maximum concentration values for certain hazardous substances in electrical and electronic equipment [2005/618/EC Maximum Concentration Values (MCV).] This is more succinctly referred to as the RoHS Directive.

RoHS will apply to medical devices. As indicated previously, the Europa web site provides useful and extensive links on this, including frequently asked questions and the Recast proposals for both RoHS and WEEE Directives announced in December 2008. Please see:

http://ec.europa.eu/environment/waste/weee/index_en.htm

The proposed Recast of the RoHS brings electro-medical devices of all types within the scope of the RoHS Directive; these will be introduced as follows:

- Medical devices subject to the MDD, 93/42/EEC by 1 January 2014;
- In vitro diagnostics subject to the IVDD, 98/79/EC by 1 January 2016;
- Active implantable medical devices will continue to be exempt until at least 2020, when the Commission will be required to review their exclusion.

Manufacturers should now consider how this will affect current products and what actions will be necessary. The design of all new products should now take into account the impact of the RoHS to ensure the minimum of redesign at a later date. Substances to avoid include cadmium, lead, mercury, hexavalent chromium, polybrominated biphenyls (“PBBs”), and polybrominated diphenyl ethers (“PBDEs”); it should be noted that the Commission has the power to add additional substances following procedures as stated in the “REACH” regulation (discussed in the next section). It should be noted that REACH and RoHS will both continue to be applied. It is possible that data gathered via REACH compliance may be used to justify additional banning of substances under RoHS. The RoHS banned substances are also listed in the REACH candidates of very high concern, requiring market authorisation and having restrictions on their use.

HBCDD and phthalates [Hexabromocyclododecane (“HBCDD”), Bis (2-ethylhexyl) phthalate (“DEHP”), Butyl benzyl phthalate (“BBP”), and Dibutylphthalate (“DBP”)] listed in Annex III of the RoHS proposal are priority substances for the Commission to consider banning, using the RoHS, and these are also substances listed within the REACH candidate list of substances of very high concern for authorisation. The above indicates how REACH and RoHS are set up to work in parallel and to complement each other. The need to label medical devices using phthalates and to justify their use with pregnant or nursing women and in the treatment of children is also raised in the MDD Revision (section 7.5).

Annex VI of the RoHS proposal exempts many uses of lead in medical applications where there are no practical alternatives such as X-ray shielding, some MRI components and counterweights. Lead in some medical soldering applications is also allowed, including that for bonding ultrasonic transducers. Further exemptions may also be granted if, “the availability and reliability of substitutes is not ensured,” and if these can take into account “socio-economic” factors when providing a justification.

It should be noted the RoHS proposal provides a possible exemption from REACH authorisation procedures for those substances with a RoHS exemption. Such an exemption, strictly speaking,

applies to substances in the manufacturing process, since REACH registration requirements do not apply to articles but to the substances contained in articles.

It is important to note that affixing the CE marking to a product will require the legal manufacturer to ensure the product is in compliance with the RoHS. For Notified Bodies and Competent Authorities this will require additional checking of the technical documentation.

REACH

REACH stands for the Regulation on Registration, Evaluation, Authorisation and Restriction of Chemicals; it is intended to ensure the protection of human health and the environment from the risks that can be posed by chemicals. The formal regulation title of the 849 page document is:

Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC.

REACH applies to all types of medical devices, including IVDs; it is a major regulation that affects all manufacturing sectors including the supply chain. Manufacturers should review whether this affects them or their supply chain and if it is likely that it will eventually affect something. Where applicable, there will be a need to assess products and register those sold. Users will need to be warned of risks. Please see:

http://ec.europa.eu/environment/chemicals/reach/reach_intro.htm;

http://ec.europa.eu/enterprise/reach/index_en.htm;

http://echa.europa.eu/home_en.asp (ECHA).

It is recommended that manufacturers consider taking specialist advice concerning REACH; the regulations can prove to be complex and can require significant resources to achieve full compliance, especially if a full environmental impact assessment is required. The REACH Competent Authority is the European Chemicals Agency (ECHA) and the website link indicated above has numerous guidance documents as well as an on-line tool known as “Navigator,” to help enquirers determine their obligations under REACH. It is recommended that Navigator be used as part of a review process for each substance.

ECHA has issued a list of priority substances for discussion that will require authorisation and this list is available at

http://echa.europa.eu/consultations/authorisation/draft_recommendations/prioritisations_en.asp

This list includes phthalates (DEHP, DBP, BBP and the flame retardant HBCDD). The phthalate DEHP is used in many medical devices as a plasticiser or softener. Whilst the use of such substances can be justified in many cases, the science behind this categorisation is questionable. It is probably better to avoid such substances where there is an acceptable alternative. Stakeholders had until 14 April 2009 to comment. The AIMDD/MDD Revision requires that medical devices used to transport fluids to or from the body to be appropriately labeled as containing phthalates. The use of phthalates in devices intended to be used in the treatment of children, pregnant or nursing women requires justification and the instructions for use must provide information on residual risks and on any precautionary measures required.

New Waste Directive

Other directives that may apply include those concerning waste and the environment. Directive 2008/98/EC of the European Parliament and the Council of 19 November 2008, on waste and on repealing certain Directives is sometimes referred to as the new waste directive. According to the Commission, it revised the Directive 2006/12/EC on waste in order to modernise and streamline its provisions. It "...sets the basic concepts and definitions related to waste management and lays down waste management principles such as the "polluter pays principle" or the "waste hierarchy"."

Directive 2008/98/EC is a framework directive and the transition period ends on the 12 December 2010, when it replaces the following Directives:

- Council Directive 75/439/EEC of 16 June 1975, on the disposal of waste oils
- Council Directive 91/689/EEC of 12 December 1991, on hazardous waste
- Directive 2006/12/EC of the European Parliament and of the Council of 5 April 2006, on waste

Directive 2008/98/EC defines hazardous waste, including infectious waste as

‘Infectious’ substances and preparations, containing viable micro-organisms or their toxins, which are known or reliably believed to cause disease in man or other living organisms.

MDD and IVDD Annexes

The **MDD** contains several recitals, 23 Articles and 12 Annexes:

- Annex I lists 14 essential requirements and 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 **IVDD** is very similar to the MDD. It contains similar language and structure to the MDD with several recitals, 24 Articles and 10 Annexes. These cover much of the same effective content as the MDD, especially from a quality systems standpoint and should now be familiar to most well-established medical device companies based in Canada who export to Europe, and especially for those already selling in compliance with the MDD or AIMDD.

- Annex I lists eight 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 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.
- Annex X, CE Marking of Conformity is almost identical to MDD Annex XII.

The IVDD, 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.

The CE marking, and how to apply it, is described in Annex XII of the MDD and Annex X of the IVDD.

1 Key Elements of the MDD and IVDD

1.1 Essential Requirements

Annex I of the MDD identifies 14 essential requirements and 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 (ER) cover patient safety, product performance, safety in use, transportation and storage, risks and benefits, and design and construction requirements.

These requirements have been revised in the MDD Revision and have strengthened or reinforced the requirements for several items. These changes include the need to do the following:

- reduce risks from ergonomic design taking into account the knowledge, experience, education and training of users (ER 1);
- demonstrate conformity with the ERs; this must include a clinical evaluation (ER 6a.);
- get a scientific opinion on the quality, safety, benefit/risk ratio and usefulness of any ancillary medicines or blood derived products used (ER 7.4);
- ensure that the risk from substances that are carcinogenic, mutagenic or toxic to reproduction are minimised and products labeled accordingly (ER 7.5);
- in the case of devices intended to be used for the treatment of children or pregnant women or nursing women, the manufacturer must justify the use of any carcinogenic, mutagenic or toxic substance and label the products accordingly (ER 7.5);
- validate software according to the state of the art taking into account the principles of development lifecycle, risk management, validation and verification (ER 12.1a);
- ensure that each device is supplied with the information needed to use it properly, taking into account the training and knowledge of potential users (ER 13.1);
- provide consistent labeling across the EU, for products indicated to be for single use (ER 13.3 (f));
- provide information characteristics and technical factors for single use devices about the consequences of reusing such devices (ER 13.6 (h)); and
- include the date of issue or the latest revision of the instructions for use.

All the applicable ERs need to be complied with and proof provided in the technical file on how this has been achieved.

Annex I of the IVDD lists eight essential requirements (ERs), each with a number of subsets that have a very similar scope to that of the MDD. The IVDD does have some specifically IVD

related requirements concerning confounding factors, reagent composition, analytical performance characteristics and self-testing devices.

For higher risk devices listed in Annex II, list A of the IVDD concerning products for blood grouping testing, HIV 1 & 2, HTLV (1 & 2) and hepatitis B, C and D testing there are additional requirements beyond the ERs that are applicable and these are given in a document often referred to as the 'CTS'. The first CTS was the Commission Decision of 7 May 2002, on common technical specifications for in vitro diagnostic medical device (2002/364/EC). This has been amended by the following:

Commission Decision of 3 February 2009, amending Decision 2002/364/EC on common technical specifications for in vitro diagnostic medical devices (2009/108/EC)

The CTS indicates the general principles, methods and number of tests required to achieve compliance. These products are also subject to batch release procedures controlled by a notified body. It should be noted that homogeneous batches are defined in MEDDEV 2.5/6 Rev.1 (February 1998) available at http://ec.europa.eu/consumers/sectors/medical-devices/documents/guidelines/index_en.htm.

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. This is a risk-based system with Class I posing the least risk, Class III the highest risk, with Class IIa and IIb representing medium to high risk devices. If more than one classification rule applies to a device, the strictest rules resulting in the higher classification determines the device classification.

Guidance is provided in the classification MEDDEV provided in two parts at http://ec.europa.eu/consumers/sectors/medical-devices/documents/guidelines/index_en.htm.

MEDDEV 2.4/1 Rev.9 (June 2010) Guidelines for the Classification of Medical Devices

Guidance is also provided at the 'Borderline and classification issues' web page: http://ec.europa.eu/consumers/sectors/medical-devices/documents/borderline/index_en.htm.

This includes the Manual on Borderline and Classification in the Community Regulatory Framework for Medical Devices Version 1.4 (05-2009).

The IVDD 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. This means the majority of IVDs do not require the intervention of a notified body (NB) but the requirements of Annex III EC Declaration of Conformity must be fully met and can be examined by the Competent Authority (CA) where the devices are registered.

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 IVDD. 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 IVDD, 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 Canadian regulations require the use of a quality system to ISO 13485 and this is discussed in the next chapter. The US Food and Drug Administration (FDA) demand it for most Class II and all Class III devices, and all devices that have software – including Class I devices. Both EN ISO 9001: 2008 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), required by Canadian regulations and is the global quality standard for all forms of medical devices.

1.4 Technical Documentation

For both the MDD and IVDD, 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, the level of documentation completed is often similar to that for the full quality system approach recommended in the previous section.

The key requirements are made clear in Annex VII of the MDD and Annex II of the IVDD EC Declaration of Conformity. Complying with these requirements and the Essential Requirements of Annex I (MDD & IVDD) is the heart of the CE marking process.

Recommendation NB-MED/2.5.1/Rec5 Technical Documentation is available from the European Association of Notified Bodies for Medical Devices at: www.team-nb.org. This link contains really important guidance that all manufacturers that should follow. Other useful guidance is available from the web site, although some care should be taken in selecting what is used.

1.5 Declaration of Conformity

A written declaration of conformity to the MDD or IVDD is required from the manufacturer prior to affixing the CE marking on the product. This is required for all medical devices whatever conformity assessment route is used and its contents should include:

- Manufacturer's name and address;
- European Authorized Representative's name and address;
- Notified Body's name and address, if required;
- Name of the device, including model number and trade name;
- Serial/Batch No. - where this is useful to identify European product, or required;
- Conformity assessment procedure (route) to compliance including applicable annexes, and device classification, including any certificate numbers. State the rule number for the classification of MDD devices that applies;
- Identification of the applicable directive;
- Certification number of the quality system, if applicable;
- Reference to the technical file that needs to include a list of standards; and
- Name and signature, including the date signed, of an appropriate representative of senior management.

Reference to records certifying compliance with specifications and a list of standards are optional but are sometimes included by manufacturers. A list of standards is useful when added to the Essential Requirements Checklist or Assessment.

Some general background and applicable standards for the EC Declaration of Conformity is available in the "Blue Guide" referred to earlier as, "The Guide to the Implementation of Directives Based on New Approach and Global Approach" available from <http://ec.europa.eu/enterprise/policies/single-market-goods/documents/blue-guide/>

This is expected to be updated as it is now very dated. The Declaration of Conformity is a legal document that indicates the person signing it is satisfied that all requirements of the applicable directives have been satisfied. EN ISO/IEC 17050-1:2004 Conformity assessment. Supplier's declaration of conformity. Part 1: General requirements, provides some insights too.

1.6 Post-Market Surveillance

For both the MDD and IVDD, the manufacturer is required to be proactive in monitoring post-production performance of their products. This includes gathering good and bad information gained from market experience and clinical use.

The MDD Revision now requires manufacturers to consider the provisions of Annex X Clinical Evaluation as part of the required "systematic procedure to review experience gained from devices in the post-production phase," and in Annex X 1.1c it states the "...clinical evaluation

and its documentation must be actively updated with data obtained from the post-market surveillance. Where postmarket clinical follow-up, as part of the postmarket surveillance plan for the device, is not deemed necessary this must be duly justified and documented.”

The IVDD 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; all must be in a standardized format. More on this database, known as Eudamed is covered later in section ‘2.3 Applying for Registration.’

Vigilance is a very important part of postmarket surveillance and is covered in the next section.

1.7 Vigilance Reporting

For both the MDD and IVDD, 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. An important guidance document was published during 2007 that included significant changes concerning the need to report incidents immediately and more: MEDDEV 2.12-1 rev 6 (December 2009) Guidelines on Medical Devices Vigilance System. This is essential for all manufacturers to comply with. It is available at http://ec.europa.eu/consumers/sectors/medical-devices/documents/guidelines/index_en.htm.

1.8 European Authorised Representative

Manufacturers with offices in Europe will normally choose to be their own ‘authorised representative,’ although they can choose an alternative. Article 10 of the IVDD 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 authorised representative has to inform the competent authority of the member state where they are located and provide contact details.

Note the IVDD modifies the MDD and defines an authorised 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.”

The MDD Revision makes it clear that only one Authorised Representative, at least per product group, is permissible under modified Article 14. Where a manufacturer does not have a registered place of business in the European Community the name and address of the authorised representative must appear on the label or the outer packaging or the instructions for use.

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 least stringent (Class I) to the highest 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 Procedure (Route)

The conformity assessment procedures (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, and are not allowed to carry the CE marking.

The choice of conformity assessment will often depend on whether the company is a start-up or an established company. The EU New Approach is flexible and there are options which suit start-ups, as a fully certified quality system may not be needed for initial CE marking, although many elements of a quality assurance system are required. Some large scale devices may also be CE marked more appropriately using a type test or product quality certification. However, all manufacturers are recommended to work towards and ultimately achieve certified compliance to ISO 13485: 2003.

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 Class I devices with a CA and other product classifications through the NB. 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.

The contact information for all Competent Authorities is available through the useful links page on the Europa web site. Go to http://ec.europa.eu/consumers/sectors/medical-devices/links/index_en.htm and then click on National Competent Authorities contact points:

http://ec.europa.eu/enterprise/sectors/medical-devices/files/list-of-contact-points-within-the-national_en.pdf

Including one specifically for vigilance purposes:

http://ec.europa.eu/enterprise/sectors/medical-devices/files/list-of-vigilance-contact-points-within-the-national_en.pdf

All Notified Bodies contact points are available through:

<http://ec.europa.eu/enterprise/newapproach/nando/index.cfm?fuseaction=directive.main>

Note the IVDD modifies the MDD.

This requirement also has relevance to the MDD and is modified via the IVDD under ‘Article 21 Amendment of directives.’ This section of the IVDD lists a number of modifications to the MDD in regard to definitions, the European databank and particular health monitoring measures. It is 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/or possibly your Authorised Representative (if you use one) so the next section has been included to provide more information.

European Databank and Global Medical Device Nomenclature System (GMDN)

The European Databank is covered in Article 14a and will store regulatory information that will be available to CAs but not the public. This information will include registration of manufacturers and their authorised representatives, but exclude data on custom-made devices. It will include data on certificates issued, modified, supplemented, suspended, withdrawn or refused; vigilance data, and data concerning clinical investigations.

It is supposed to be implemented no later than 5 September 2012.

This database is known as Eudamed and is already being used by a number of CAs and obligatory use is “foreseen for May 2011” by the Commission. Please refer to the following link for more information:

http://ec.europa.eu/consumers/sectors/medical-devices/market-surveillance-vigilance/eudamed/index_en.htm

The use of ‘GMDN’ in Eudamed is indicated here:

“An important tool for Eudamed is the Global Medical Device Nomenclature (GMDN). The development of GMDN started with a mandate to CEN for the development of a structure for a medical device nomenclature. The result, the European standard EN ISO 15225 "Nomenclature - specification for a nomenclature system for medical devices for the purpose of regulatory data exchange", was further developed into a CEN technical report. Maintenance of this work was taken over by the [GMDN Maintenance Agency](#) which developed the Nomenclature (referred to as GMDN) into what it is today, a comprehensive, regularly updated web-based nomenclature accessible to manufacturers against license fees. GMDN presents the best practice for Eudamed purposes, even though, for the time being, data entry is also possible without providing a GMDN code.”

The GMDN is a system for providing common descriptions of medical devices. It is currently being implemented across Europe but each country’s implementation timetable differs 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 Maintenance Agency web site www.gmdnagency.com already indicated above. A fee is required to use the GMDN codes but this may well change. Manufacturers should check the web site for more fee details as they depend upon the type of entity using them and the number of codes required.

2.4 Provide Technical Documentation

Technical documentation is examined by the NB and must demonstrate that the quality system and/or products comply 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) 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 declaration) to provide false or misleading information on a Declaration of Conformity. The content of this was covered earlier in section 1.5. The declaration should be signed by a senior officer of the company.

2.6 Affix the CE Marking

For class I devices that are not intended to perform a measuring function or to be sterile, the CE marking can be applied after the Declaration of Conformity has been completed and signed. 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. With higher risk devices and those with integral medicinal or blood derivative products this can be considerably longer.

3 What Each Step Involves - MDD

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 this guide. Medical devices are classified according to their intended use. Annex IX Classification Criteria 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, when required, early in the process assists manufacturers to verify the appropriate device class.

‘MEDDEV 2.4/1 Rev.9 (June 2010) 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 on

http://ec.europa.eu/consumers/sectors/medical-devices/documents/guidelines/index_en.htm

MDD Revision – note that this changes some classification rules

It is very important to note that the MDD Revision has changed some of the classification rules and that any additional requirements that result must be addressed by 21 March 2010.

Changes to Definitions and Implementing Rules

Stand alone software is now considered to be an active medical device.

The definition of the central circulatory system has been extended by the MDD Revision to include the arcus aorta, aorta descendens to the bifurcation aortae. This change may affect the classification of some devices as given in Annex IX Classification Criteria. The central circulatory system is now defined as the following vessels:

“arteriae pulmonales, aorta ascendens, arcus aorta, aorta descendens to the bifurcatio aortae, arteriae coronariae, arteria carotis communis, arteria carotis externa, arteria carotis interna, arteriae cerebrales, truncus brachiocephalicus, venae cordis, venae pulmonales, vena cava superior, vena cava inferior.”

Section 2.6 defines continuous use as “an uninterrupted actual use of the device for the intended purpose” and if the use is discontinued in order for the device to be immediately replaced by another of the same type, it shall be considered an extension of the continuous use of the device.

Changes to Rules

Rule 5: The first sentence has been expanded:

“All invasive devices with respect to body orifices, other than surgically invasive devices and which are not intended for connection to an active medical device or which are intended for connection to an active medical device in Class I.”

Rule 13: Reference to medicinal directive 65/65//EEC replaced by 2001/83/EC:

“All devices incorporating, as an integral part, a human blood directive are in Class III.”

Rule 15: The following has been added to the second paragraph:

“Unless they are specifically to be used for disinfecting invasive devices in which case they are in Class IIb.”

Rule 16: “Non-active devices” replaced by “Devices” to reflect the technology progression that now allows X-rays to be captured in active devices, as well as conventional non-active plates.

3.2 Choosing the Conformity Assessment Route

Each device class offers different conformity assessment routes for 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 - Full Quality Assurance System, III - Type Examination, IV - Product Verification, V - Production Quality Assurance, VI - Product Quality Assurance and VII - Declaration of Conformity of the MDD.

For Class I devices, Annex VII must be applied.

Useful insights and guidance concerning Class I medical device registration is available in English from the UK CA, the Medicines Healthcare and product Regulatory Agency (MHRA): <http://www.mhra.gov.uk/Howweregulate/Devices/Registrationofmedicaldevices/index.htm>

The MHRA has more links for guidance concerning the MDD available at <http://www.mhra.gov.uk/Howweregulate/Devices/MedicalDevicesDirective/index.htm>

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.

3.2.1 Class I Device

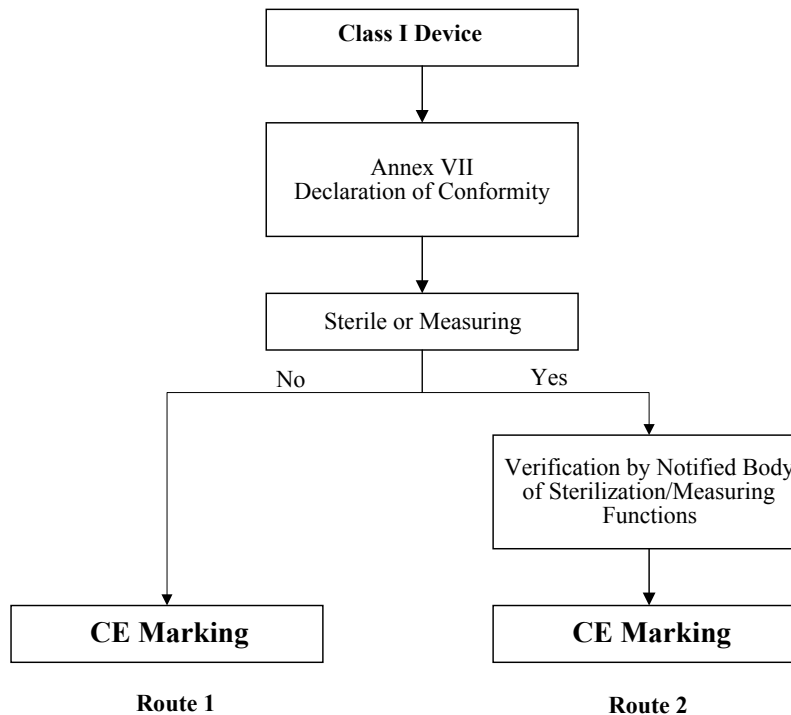


Figure 1: Conformity Assessment Procedures – Class I Devices

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 (Annex VII, section 1).

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 (Annex VII, section 2).

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

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 comply with the MDD (Annex VII, section 5). This requirement can be achieved using one of the procedures from Annex II, IV, V or VI. [*Annex II allowed by the MDD Revision.*]

3.2.2 Class IIa Device

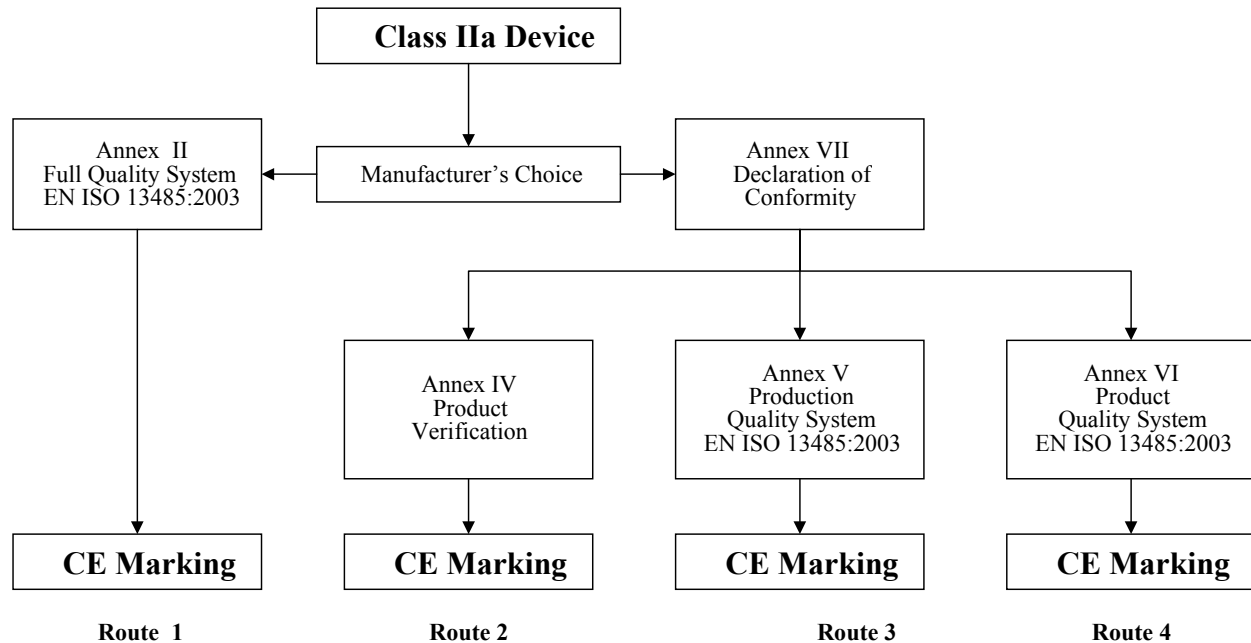


Figure 2: Conformity Assessment Procedures – Class IIa Devices

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. The MDD Revision now demands the NB “...shall assess, as part of the assessment in Section 3.3, the technical documentation as described in Section 3.2(c) for at least one representative sample for each device subcategory for compliance with the provisions of this Directive.”

Manufacturer makes written declaration of conformity and affixes CE marking. This includes the design of product.

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

Route 2: Application of Annex VII with Annex IV

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

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

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

Manufacturer declares that the product complies with the technical documentation as referred to above (Annex VII, section 3) and in the MDD (Annex IV, section 8.1).

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

Route 3: Application of Annex VII with Annex V

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

NB approves quality system to Annex V of the MDD, using EN ISO 13485: 2003, including any justified exemption from product realization (Annex V, section 1). The MDD Revision now demands (section 6) the NB "...shall assess, as part of the assessment in Section 3.3, the technical documentation as described in Section 3 of Annex VII for at least one representative sample for each device subcategory for compliance with the provisions of this Directive."

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

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

Route 4: Application of Annex VII with Annex VI

Manufacturer provides technical documentation to demonstrate the product's compliance with the MDD (Annex VII, section 2). The MDD Revision now demands (Section 6) the NB "...shall assess, as part of the assessment in Section 3.3, the technical documentation as described in Section 3 of Annex VII for at least one representative sample for each device subcategory for compliance with the provisions of this Directive."

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

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

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

For all Class IIa Routes

The technical documentation, including certificates and product records indicated in Annex II section 6 must be kept for at least five years after the last product has been manufactured and at least for fifteen years in the case of implantable devices in the teeth.

Any significant changes require approval by the NB.

3.2.3 Class IIb Device

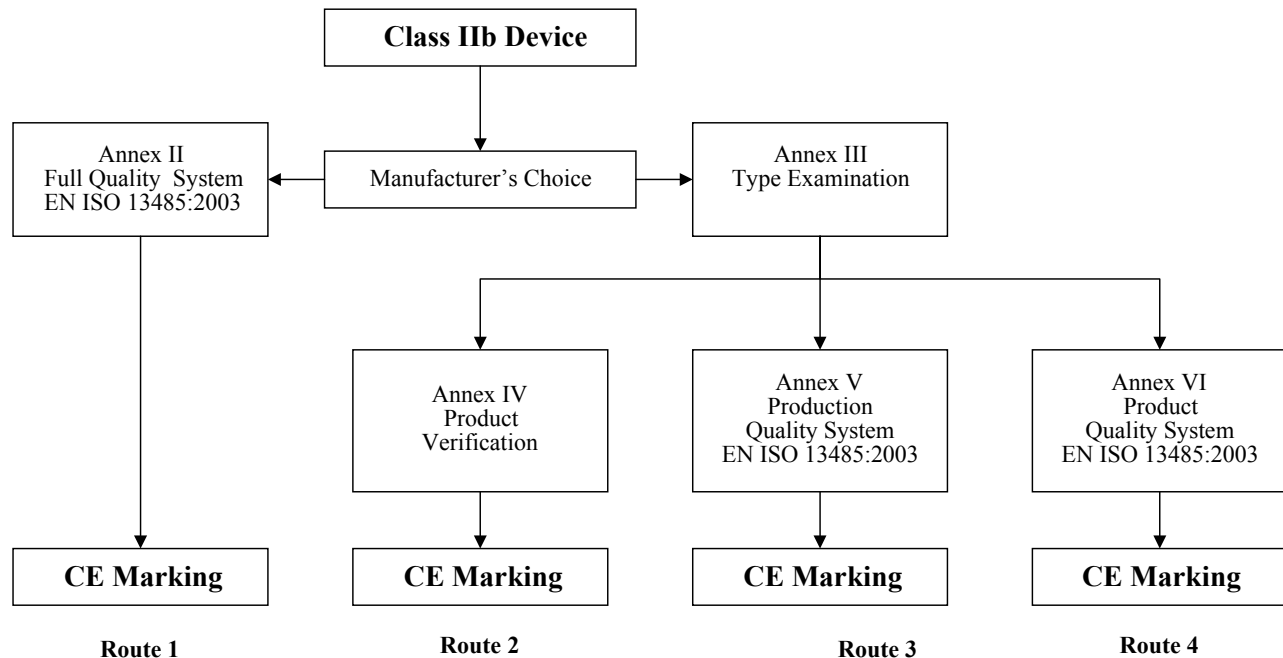


Figure 3: Conformity Assessment Procedures – Class IIb Devices

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

This is the same as in Route 1 for Class IIa devices. The MDD Revision now demands (Section 6) the NB “...shall assess, as part of the assessment in Section 3.3, the technical documentation as described in Section 3.2(c) for at least one representative sample for each generic device group for compliance with the provisions of this Directive.”

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 (Annex III, section 3).

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 (Annex III, sections 4 & 5).

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

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

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

Manufacturer institutes procedures to undertake post-market surveillance and vigilance reporting to national authorities (Annex IV, section 3). Any significant product changes require approval by the NB.

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 (Annex III, section 2).

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 (Annex III, sections 4 & 5).

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

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

Manufacturer institutes procedures to undertake post-market surveillance and vigilance reporting to national authorities (Annex V, section 3.1). Any significant product changes require approval by the NB.

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 (Annex III, section 2).

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 (Annex III, sections 4 & 5).

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

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

Manufacturer institutes procedures to undertake post-market surveillance and vigilance reporting to national authorities (Annex VI, section 3.1). Any significant product changes require approval by the NB.

For all Class IIb Routes

The MDD Revision (Annex X, section 1.1a) for implantable devices expects that a clinical investigation (trial) be undertaken, unless not doing so can be scientifically justified.

The technical documentation, including certificates and product records indicated in Annex II section 6 must be kept for at least five years after the last product has been manufactured and at least for fifteen years in the case of implantable devices.

Any significant changes require approval by the NB.

3.2.4 Class III Device

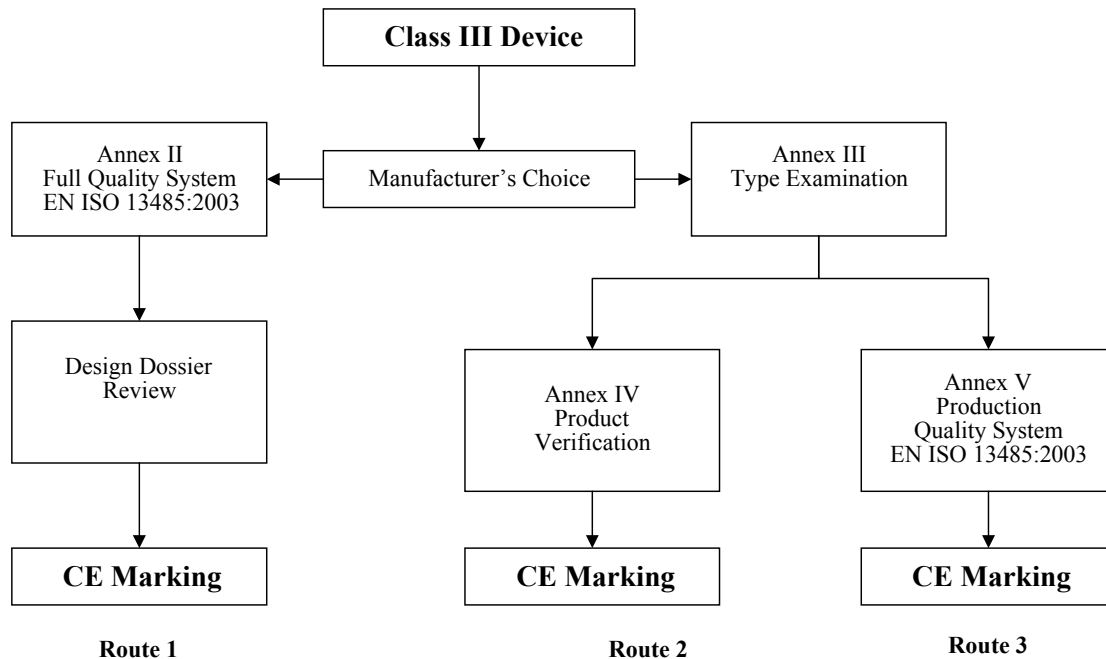


Figure 4: Conformity Assessment Procedures – Class III Devices

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 (Annex II, section 1).

NB examines the Design Dossier technical documentation related to product design, manufacture and performance to assess compliance with MDD and issues an EC design examination certificate (Annex II, section 4). (See also the Design Dossier section later).

Manufacturer makes written Declaration of Conformity and affixes CE marking (Annex II, section 2).

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

Route 2: Application of Annex III with Annex IV

This is the same as Route 2 for Class IIb devices. The manufacturer informs NB about batch release of products with human blood derivatives and sends NB the appropriate certificates.

Route 3: Application of Annex III with Annex V

This is the same as Route 3 for Class IIb devices. The manufacturer informs NB about batch release of products with human blood derivatives and sends NB appropriate certificates.

For all Class III Routes

The MDD Revision requires the NB to get a scientific opinion on the quality, safety, benefit/risk ratio and usefulness of any ancillary medicines or blood derived products used (ER 7.4).

The MDD Revision also adds the need for a statement on whether or not the device incorporates a medicinal substance or blood derivative referred to in Section 7.4 of Annex I. This has to include the opinion of the appropriate Competent Authority (CA or EMEA) as given in the expanded Annex II, section 3.2(c) referred to above. Annex II, section 4 (Annex III, section 5) indicates this opinion must be provided by the appropriate Competent Authority within 210 days of them receiving valid documentation. For devices incorporating blood derivatives, the NB may not deliver the design examination certificate if the EMEA's opinion is unfavourable.

Where a device incorporates a medicine or human blood derivative product, the manufacturer must inform the NB of the release of the batch and send it the official certificates issued by a State or designated laboratory.

In borderline classifications, where medical devices utilise medicinal product(s) covered by Directive 2001/83/EC, the decision as to which classification a product falls under shall take particular account of the principal mode of action of the product. (See Article 1 Section 5(c))

A statement is required indicating whether or not the device is manufactured utilising tissues of animal origin as per Directive 2003/32/EC.

It is expected by the MDD Revision (Annex X, section 1.1a) that a clinical investigation (trial) is undertaken for all implantable devices and Class III devices, unless not doing so can be scientifically justified.

The technical documentation, including certificates and product records indicated in Annex II, section 6 must be kept for at least five years after the last product has been manufactured and for at least fifteen years in the case of implantable devices.

Any significant changes need to be approved by the NB.

3.3 The Registration Process

3.3.1 Selecting a Notified Body

The registration, or audit, process for the conformity assessment is similar to that used for ISO 9001 registration. Only 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 9001/EN 13485 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. Contact points for Notified Bodies are available through:

<http://ec.europa.eu/enterprise/newapproach/nando/index.cfm?fuseaction=directive.main>

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 the 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).

The **MDD Revision** now requires NBs to examine the technical documentation of Class IIa devices "...for at least one representative sample of each device subcategory for compliance..." For Class IIb devices the NB is required to examine the technical documentation "...for at least one representative sample of each generic device group for compliance..." In choosing the samples the NB has to take into account the "...novelty of the technology, similarities in design, technology, manufacturing and sterilisation methods, the intended use and the results of any previous relevant assessments (e.g. with regard to physical, chemical or biological properties) that have been carried out..." This adds time to audits and will increase charges but is mandatory.

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 with approximately 30 employees, manufacturing a Class IIa or IIb device would be required to pay in the range of \$30,000 to \$35,000 Canadian for a quality system certification (full quality system route). This cost estimate includes travel and semi-annual or annual surveillance audits for three years. Class III devices require a Design Dossier review, which would add approximately \$8,000 per Design Dossier. Where there is a requirement for a type examination test, the cost would depend upon the type of testing to be conducted.

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 at least three NBs, listing the criteria upon which they will be selected. A sample questionnaire is attached as Appendix 2. It is also important to select a 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 up to \$5,000 Canadian 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 when following Annex II, the manufacturer must receive two certificates from an NB: a) one relating to the quality system and b) the EC Design-Examination Certificate. Alternatives include type examination that requires certification coupled with either Annex V Production Quality System or Annex IV Product Verification.

All conformity assessment routes for Class II and III devices require at least a sample of the design to be examined by a NB.

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 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 or working towards using it. EN ISO 13485: 2003 is the harmonised quality system standard for all medical device directives.

The NB that approved the quality system must be informed by the manufacturer of any plan for substantial changes and these plans and the implementation of them will require assessment.

As already indicated and being important to note here, the MDD Revision now requires manufacturers to consider the provisions of Annex X Clinical Evaluation as part of the required “systematic procedure to review experience gained from devices in the post-production phase,” and in Annex X 1.1c it states the “...clinical evaluation and its documentation must be actively updated with data obtained from the post-market surveillance. Where post market clinical follow-up as part of the post-market surveillance plan for the device is not deemed necessary, this must be duly justified and documented.”

Record Retention

The manufacturer (or its authorised representative – not recommended) must keep a copy of all quality records for at least five years after the last device has been manufactured and, following the MDD Revision, for at least fifteen years for implantable devices. This documentation includes:

- Declarations of Conformity
- Quality system documentation and changes (see Annex II section 3.1 and 3.4)
- Quality records from design to final inspection (see Annex II section 3.2)
- Design of the device (see Annex II section 4.2)
- Certificates, assessments and inspections by NBs (see Annex II sections 3.3, 4.3, 4.4, 5.3 and 5.4)

3.4.2 Product Documentation

Technical documentation is required for all medical devices to support product compliance with the MDD. 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 Annex X, section 3 of the MDD and is listed in section 3.4.2.2. 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.

Recommendation NB-MED/2.5.1/Rec5 Technical Documentation is available from the European Association of Notified Bodies for Medical Devices at: www.team-nb.org. This contains really important guidance for all manufacturers that should be followed. Other useful guidance is available from the web site, although some care in selecting what to use is required.

This NB-MED covers technical files and Design Dossiers. A Design Dossier is used to refer to a technical file for Class III devices that have the most comprehensive requirements.

Technical files are required for all medical devices and all manufacturers should examine the Design Dossier requirements for guidance as what to consider. The core of the technical file is to demonstrate how the Essential Requirements (ERs) of Annex I have been met.

The contents of a technical file should follow the NB-MED/2.5.1/Rec5 Technical Documentation (as indicated above), namely the Part A and B of the technical documentation.

Part A (summary) should consist of the following (please see Annex VII of the MDD):

- Manufacturer's name and address.
- Name of the device, including model number and trade or proprietary name.
- Name and address of facilities involved in the design and manufacture of the device(s).
- Notified Body's name and address, if required.
- Identification of the applicable directive(s) and regulations.
- Conformity assessment procedure (route) to compliance including applicable annexes, and device classification. State the rule number for the classification of MDD devices that applies.
- Certificates relating to the quality system and/or design or type examinations, if applicable.
- Declaration of conformity to the applicable directive.
- A brief description of the device(s) that should include the intended purpose(s) and indications for use, together with a list of accessories. This should include any variants that are planned.
- In the case of products provided in a sterile condition, a statement about methods used and

reference to a validation report.

- Labels and instructions of use (where applicable). [Marketing materials are worth including too.]
- Identification of technical standards with which compliance is claimed and reference to any third party certifications.
- A statement about pre-clinical or bench testing and clinical data obtained.
- Name and signature of an appropriate representative of senior management, including the date signed.

Harmonised standards for the New Approach directives should be used to establish compliance to the ERs wherever possible and can be found at <http://ec.europa.eu/enterprise/policies/european-standards/documents/harmonised-standards-legislation/list-references/>

Part B of the technical file (it does not have to be called this) contains all the other technical documentation detailing risk analysis, test reports, quality system information, descriptions of products and processes, detailed validation, etc. This information should be in as much detail as required.

Appendix 3: Content of a Design Dossier provides a suggested list of technical documentation that a manufacturer should compile to complete a design dossier for a given product or product group. This includes the changes arising from the MDD Revision.

The language of the documentation should be in the official language of the CA or another language on which they agree. Typically Part A should be translated if required, and Part B should be accepted in the language established by the manufacturer but clearly this should be checked when starting to compile the documentation.

3.4.2.1 The Design Dossier

A technical file is required for all medical devices and the most comprehensive - a Design Dossier - is required for Class III devices. A Design Dossier describes the design, manufacture and performance of the product in question. It must include all the documents needed to assess whether or not 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.

Appendix 3: Content of a Design Dossier – Technical Documentation provides a suggested list of technical information that a manufacturer should compile to complete a Design Dossier for a given product or product group. This includes the changes arising from the MDD Revision.

3.4.2.1.1 Approach to Developing a Technical File or Design Dossier

A separate technical file or 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. However a checklist, based on the approach contained in Appendix 4: Guidance Notes on the Interpretation of the Essential Requirements (Medical Devices Directive 93/42/EEC, including the 2007/47/EEC Amendments) of the present guide, can be used to briefly summarize the basis on which a product or product group meets the ERs (e.g., reference to a harmonized standard or to a specific technical report or file).

A table is usually created listing all the ERs, whether they are applicable or not, the measures taken to address each ER and references to supporting technical documentation and location of documents. This is known as an Essential Requirements Assessment Checklist and is recommended for every product or 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 include reviews of customer complaints, draft labels, and quality system certificates, and constitute the Design Dossier for the 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 and especially not for an implantable or Class III device and with the MDD Revision is unlikely to be acceptable. As given in Annex I, in I General Requirements section 6a all Declarations of Conformity must include a clinical evaluation in accordance with Annex X Clinical Evaluations.

The revised Annex X states in section 1.1a that:

“In the case of implantable devices and devices in Class III clinical investigations shall be performed unless it is duly justified to rely on existing clinical data.”

All manufacturers should read carefully the revised Annex X and understand that regulators and NBs are paying particular attention to its requirements.

Use of harmonised standards

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. For Class III devices 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 Authorised 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 and, following the MDD Revision, for at least fifteen years for implantable devices.

3.4.2.2 Type Examination

The manufacturer must submit a product specimen or ‘type,’ along with supporting technical documentation to the NB, 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. Annex III indicates the technical documentation which must be submitted, it 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. This list is available from:

<http://ec.europa.eu/enterprise/policies/european-standards/documents/harmonised-standards-legislation/list-references/>

- Results of relevant design calculations, risk analysis, investigations, technical tests, etcetera;
- For products placed on the market in a sterile condition, a description of the methods used for sterilization;
- Proof that it conforms to the essential requirements when connected to any such device(s) if the device is to be connected to (an) other device(s) in order to operate as intended;
- 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), and relevant data. Similarly, a statement is required for the use of human blood derivatives, taking into account the intended purpose of the device;
- A statement about the use of any animal tissues as referred to in Directive 2003/32/EC is required;
- The design information and risk analysis as required by Annex I, General Requirements (Chapter I) section 2;
- The pre-clinical evaluation and clinical evaluation data referred to in Annex X; and
- Draft labeling and, where appropriate, the instructions for use.

An NB issues an EC type examination certificate after a review of the technical documentation confirms that the 'type' provided 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 takes 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, and fifteen years for implantable devices as per the MDD Revision.

The MDD Revision also requires the NB to obtain opinions from the appropriate Competent Authority, as per Annex I ERs section 7.4 for devices that incorporate medicinal or blood derivative products. For medicines the appropriate Competent Authority (CA) or EMEA can be approached; and for human blood derived product, the EMEA. This is undertaken by the NB involved in the product's assessment. The opinion of the CA or EMEA must be drawn up within 210 days after they receive valid documentation. The NB will consider the views of the CA or EMEA for medicines and inform them of its decision. The NB may not certificate the type of the device if the EMEA scientific opinion is not favourable. This information is covered in section 5 of Annex III.

For Class IIb devices type-examination can be used in conjunction with Annex IV Product Verification, or Annex V Production Quality System, or Annex VI Product Quality System.

For Class III devices type-examination can be used in conjunction with Annex IV Product Verification, or Annex V Production Quality System.

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, or at least be readily available. All files need to be readily available upon request and for an appropriate response to vigilance situations or random inspections. A copy of the summary file is normally kept by the manufacturer's designated Authorised Representative within the EU and should follow the NB-MED/2.5.1/Rec5 Technical Documentation as indicated earlier, namely Part A of the technical documentation. This needs to be kept up to date.

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 have to be made available to national authorities, upon request, within a reasonable time 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. A

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 14 June 1998, all medical devices sold within the EU must display the CE marking on the product or on its sterile pack, where practical, and also 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 IIa, IIb and III devices, the CE marking must be followed by the identification number of the NB issuing the certificates as per Article 17.

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 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.

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 where it 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 IVDD

4.1 Classify Your Product

The IVDD 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; and
- 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 IVDD.

The European Commission provides IVD guidance documents, MEDDEVs at:

http://ec.europa.eu/consumers/sectors/medical-devices/documents/guidelines/index_en.htm

These include:

- MEDDEV. 2.14/1/1 rev.1 (January 2004) IVD Guidance: Borderline Issues.
- MEDDEV. 2.14/2 rev.1 (February 2004) IVD Guidance: Research Use Only Products.

Research Use Only (RUO) products are defined; these fall outside the scope of the IVDD. Devices for performance evaluation are not RUO and should not be labelled as such and RUO must not be used to place product on the market for diagnostic testing services.

The borderline guidance provides more on RUO, general laboratory use products, invasive body contact, combination products, control materials, devices to be used by law enforcement and those intended to be used to detect chemical or biological warfare agents.

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 IVDD 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 IVDD. Their application for each 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.

The contact information for all Competent Authorities is available via the useful links page at the Europa web site:

http://ec.europa.eu/consumers/sectors/medical-devices/links/index_en.htm. Click on National Competent Authorities contact points:

http://ec.europa.eu/enterprise/sectors/medical-devices/files/list-of-contact-points-within-the-national_en.pdf

And those specifically for vigilance purposes:

http://ec.europa.eu/enterprise/sectors/medical-devices/files/list-of-vigilance-contact-points-within-the-national_en.pdf

All Notified Bodies contact points are available through:

<http://ec.europa.eu/enterprise/newapproach/nando/index.cfm?fuseaction=directive.main>

Manufacturers must also notify the CA of 'new products' [whereas clause (30)] "...with regard both to the technology used and substances to analysed or other parameters; whereas this is true in particular of high-density DNA probe devices (known as micro-chips) used in genetic screening."

Note the IVDD modifies the MDD

This requirement also has relevance to the MDD and is modified via the IVDD under 'Article 21 Amendment of directives.' This section of the IVDD lists a number of modifications to the MDD in regard to definitions, the European databank and particular health monitoring measures. It is 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 Authorised Representative (if you use one).

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

With the implementation of Eudamed, the transitional provision in Article 10 of Directive 98/79/EC, which obliges IVD manufacturers to give notification to every Member State concerned by the placing on the market of devices, will cease to apply. This should occur by the 5 September 2012, but needs to be monitored.

The UK CA (MHRA) provides useful guidance and insights concerning IVD registration and is available in English from

<http://www.mhra.gov.uk/Howweregulate/Devices/Registrationofmedicaldevices/index.htm>

- Guidance Notes for the Registration of Person Responsible for Placing In Vitro Diagnostic Medical Devices on the Market (Guidance Note 18)
- Guidance Notes on In Vitro Diagnostic Medical Devices Directive 98/79/EC (Guidance Note No. 19)
- Sale and Supply of In Vitro Diagnostic Medical Devices (Bulletin 12)

The MHRA also provides information on the EDMA IVD product classification system that can be used to register IVDs in Europe, although the intention is to use the GMDN for Eudamed as indicated for the MDD, once fully operational.

The European Commission provides IVD guidance documents, MEDDEVs at:

http://ec.europa.eu/consumers/sectors/medical-devices/documents/guidelines/index_en.htm. On this site is a form for the registration of IVDs as per Article 10 that can be used; there is also guidance on conformity assessment procedures.

Putting into service and health institutions

The IVDD also applies to a person or manufacturer who manufactures IVDs but does not place them on the market but puts “...them into service and uses them in the context of his professional activity.” (As per Article 9 section 13 of the IVDD.) This includes persons or laboratories that provide diagnostic services.

Health institutions are exempt (Article 1 section 5) from the conformity assessment requirements for devices manufactured and used only within the same health institution without transfer to another legal entity. Transfer to another legal entity is deemed to be placing on the market, whether or not this is done for free or as part of a commercial transaction. To ensure product liability is minimised and due diligence exercised such institutions are advised to follow the essential requirements of the IVDD.

Performance evaluation

Devices for performance evaluation must comply with Annex VIII Statement and Procedures concerning Devices for Performance Evaluation. This defines the content of a statement and makes it clear that the device must comply with other provisions of the IVDD apart from the performance evaluation. Performance evaluation devices do not carry the CE marking.

Products must be labelled “For Performance Evaluation Only” (ER 8.4(f)). Documentation must be kept for at least five years after the end of the performance evaluation.

The manufacturer must be registered and have a European Authorised Representative (EAR) if required and supply information to the European Databank as required.

Trade fairs and exhibitions

Devices not CE marked may be shown at trade fairs, exhibitions, scientific gatherings and similar events provided that such devices are not used on specimens taken from participants and that the product is clearly labelled or has a sign visible that indicates the device cannot be marketed or put into service until it does comply.

4.4 Provide Technical Documentation

As with the MDD, the IVDD technical documentation can be examined by both CAs and the chosen NB where applicable and must demonstrate that the quality system and/or product complies with the requirements of the IVDD. 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 IVDD. This evidence must include specific technical information, stipulated in the appropriate Annex of the IVDD to which the product will be certified.

Recommendation NB-MED/2.5.1/Rec5 Technical Documentation is available from the European Association of Notified Bodies for Medical Devices at: www.team-nb.org. This contains really important guidance for all manufacturers that should be followed. Other useful guidance is available from the web site although some care in selecting what to use is required.

The European Commission provides IVD guidance documents, MEDDEVs at: http://ec.europa.eu/consumers/sectors/medical-devices/documents/guidelines/index_en.htm as already indicated and these include:

- MEDDEV. 2.14/3 rev.1 (January 2007) IVD Guidance: Supply of Instructions for Use (IFU) and other information for *In-vitro* Diagnostic (IVD) Medical Devices.

This does allow some use of IFUs and other information supplied by the manufacturer to be provided electronically to professional users. This includes Internet use and IFUs for instruments and software for professional use.

The core of the Technical Documentation remains, as with all New Approach directives, a demonstration of full compliance with the Essential Requirements of the IVDD Annex I and as previously indicated any applicable Common Technical Specification (CTS) that apply, such as the Commission Decision, of 3 February 2009, amending Decision 2002/364/EC on common technical specifications for in vitro diagnostic medical devices (2009/108/EC).

This CTS indicates the general principles, methods and number of tests required to achieve compliance. These products are subject to batch release procedures controlled by a notified body.

It should be noted that homogeneous batches are defined in MEDDEV 2.5/6 Rev.1 (February 1998) that is available from:

http://ec.europa.eu/consumers/sectors/medical-devices/documents/guidelines/index_en.htm.

Manufacturers should examine the Product Documentation section of the MDD in this guide for more details and for the relevant guidance documents referenced here.

It should be noted that performance evaluations are expected for most IVDs.

The IVDD ERs are comprehensive and need to be addressed in detail. Use of an Essential Requirements Assessment Checklist as part of the Technical Documentation is recommended.

4.5 Make Declaration of Conformity

When a manufacturer is satisfied that a product meets all of the applicable essential requirements of the IVDD and any other applicable directives, a Declaration of Conformity covering the product is written. It is illegal for a manufacturer to provide false or misleading information on a Declaration of Conformity that is signed by an individual named person.

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 it is not a self-certifying device, before placing the device on the market, and this may take several weeks after the certification audit, allowing time for internal checking by the NB to be completed.

The CE marking is described in Annex X of the IVDD.

5 What Each Step Involves - IVDD

5.1 Classifying Your IVD

The manufacturer must first determine if the device is an IVD medical device. The IVDD definition of an ‘in vitro diagnostic medical device’ is contained in the IVDD under ‘Article 1 Scope, definitions’. Classifying an IVD is then 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 that the manufacturer discuss it with the CA or chosen NB. It is strongly recommended that all IVD manufacturers, wherever they have European offices, read the UK’s MHRA guidance notes available from

<http://www.mhra.gov.uk/Howweregulate/Devices/InVitroDiagnosticMedicalDevicesDirective/index.htm>

- 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 (Guidance Note No. 19).

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 - Declaration of Conformity, IV - Full Quality Assurance System, V - Type Examination, VI - Product Verification and VII - Production Quality Assurance of the IVDD. For most common, low-risk ‘other IVDs,’ Annex III Declaration of Conformity will be the route used.

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 can be applied.

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

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 can be applied.

Annexes IV and VII conformity assessment routes of the IVDD 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 postmarket 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 postmarket surveillance and vigilance reporting.

5.2.1 Other IVDs

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

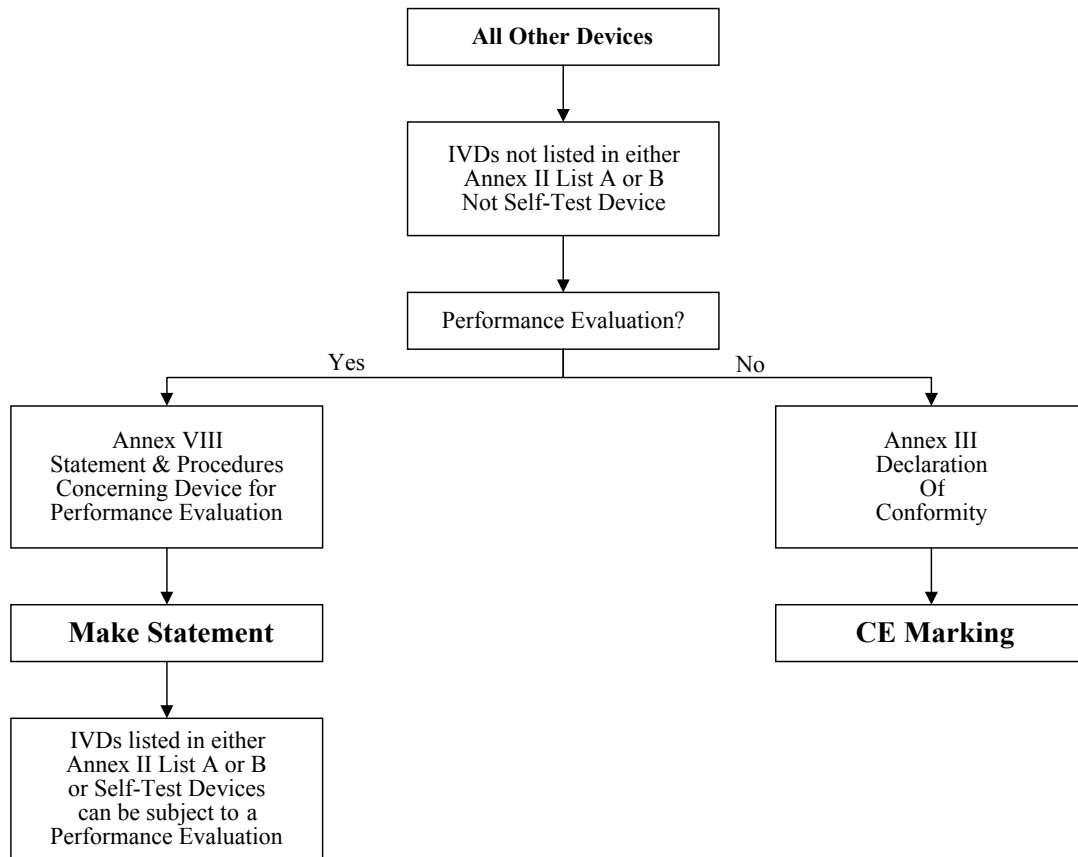


Figure 5: Other IVDs Conformity Assessment Procedures

5.2.2 Self-test IVDs

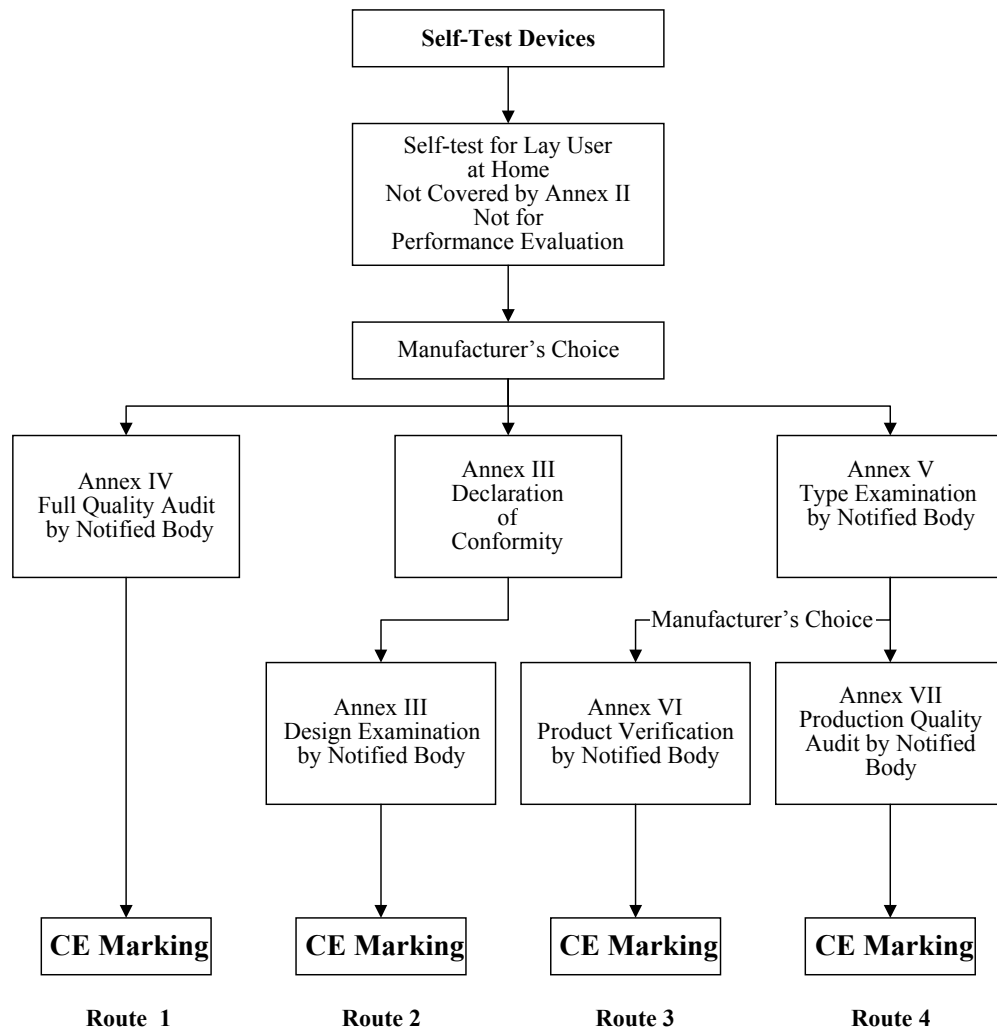


Figure 6: Self Test IVDs Conformity Assessment Procedures

Route 1: Application of Annex IV

NB approves quality system to Annex IV of the IVDD, 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 IVDD. This includes a design examination by the NB.

Annex III of the IVDD 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 IVDD. 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 has conducted tests to assess compliance of the type with the IVDD, 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 IVDD. 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 IVDD. 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 has conducted tests to assess compliance of the type with the IVDD, an EC type examination certificate is issued.

NB approves quality system to Annex VII of the IVDD, 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

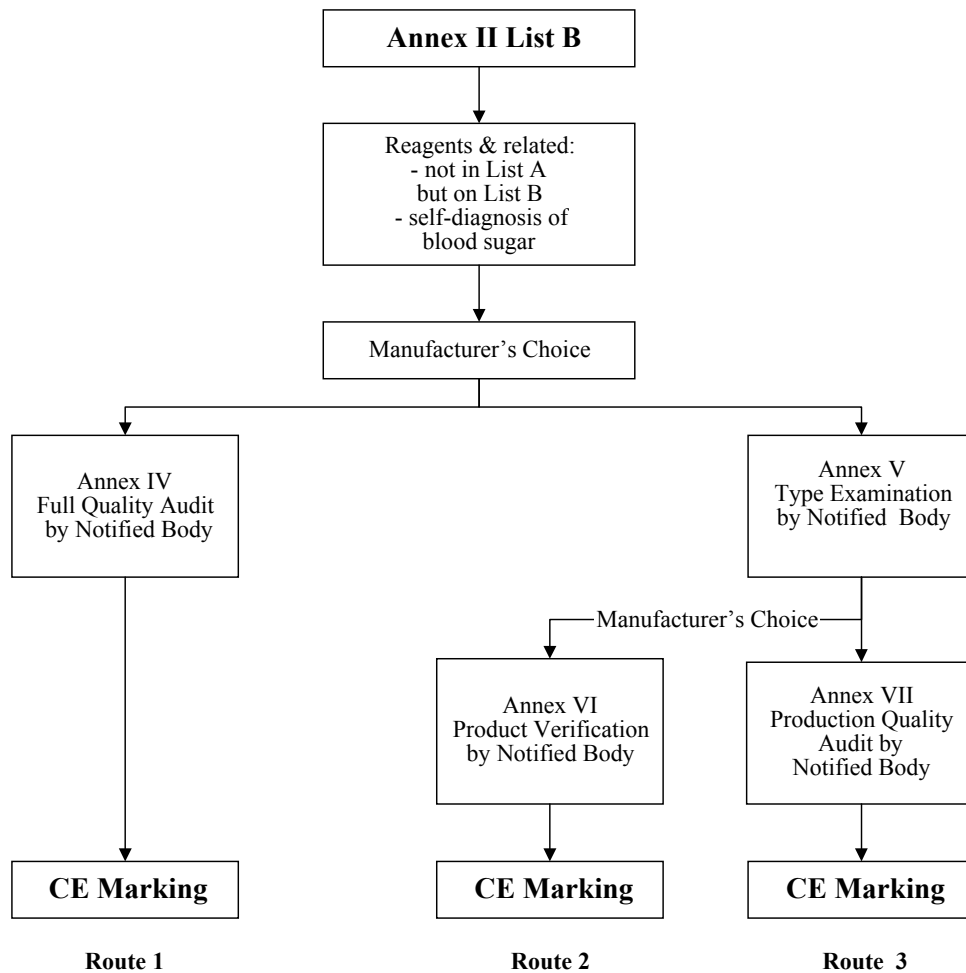


Figure 7: Annex II List B IVDs Conformity Assessment Procedures

Route 1: Application of Annex IV

NB approves quality system to Annex IV of the IVDD, 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 IVDD. 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 has conducted tests to assess compliance of the type with the IVDD, 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 IVDD. The 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 approved products and draws up certificate of conformity relating to the tests carried out.

Route 3: 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 IVDD. 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 has conducted tests to assess compliance of the type with the IVDD, an EC type examination certificate is issued.

NB approves quality system to Annex VII of the IVDD, 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

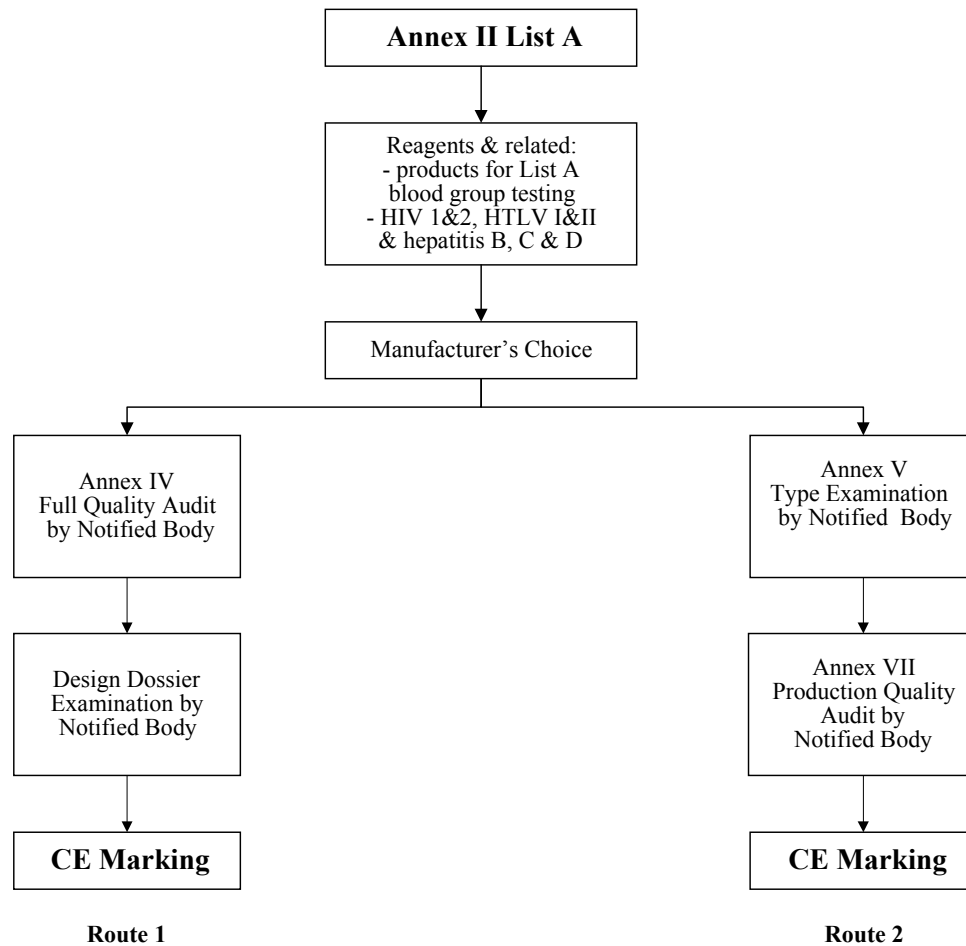


Figure 8: Annex II List A IVDs Conformity Assessment Procedures

Route 1: Application of Annex IV + Design Dossier

NB approves quality system to Annex IV of the IVDD, 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, and 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 on each batch of devices. Samples of product need to be made available to the NB in accordance with pre-agreed conditions and modalities.

The 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

The manufacturer submits a representative sample of product, or ‘type,’ to NB along with supporting technical documentation, to assess compliance of type with the ERs of the IVDD. 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 has conducted tests to assess compliance of the type with the IVDD, an EC type examination certificate is issued.

NB approves quality system to Annex VII of the IVDD, 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 on each batch of devices. Samples of product need to be made available to the NB in accordance with pre-agreed conditions and modalities.

The 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 IVDD 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 are required to 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, including clinical papers or posters.

Post-market surveillance (PMS) is required when corrective action is needed and also when nothing is wrong; both situations need to be documented. PMS is clearly very important when any customer complaint is received or on notification of an adverse incident. The handling of adverse incidents is covered in vigilance reporting requirements.

Article 2 of both the MDD and IVDD require 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 IVDD 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 CA's jurisdiction immediately. 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 provided earlier are repeated here for completeness and ease of reference. An important guidance document was published in 2007 that included significant changes concerning the need to report incidents immediately and more: MEDDEV 2.12-1 rev 5 (April 2007) Guidelines on Medical Devices Vigilance System. This is essential for all manufacturers to comply with. It is available at http://ec.europa.eu/consumers/sectors/medical-devices/documents/guidelines/index_en.htm.

The contact information for all Competent Authorities is available via the useful links page at the Europa web site:

http://ec.europa.eu/consumers/sectors/medical-devices/links/index_en.htm and then click on National Competent Authorities contact points:

http://ec.europa.eu/enterprise/sectors/medical-devices/files/list-of-contact-points-within-the-national_en.pdf

And those specifically for vigilance purposes:

http://ec.europa.eu/enterprise/sectors/medical-devices/files/list-of-vigilance-contact-points-within-the-national_en.pdf

This vigilance reporting system is somewhat similar to that of the US Medical Device Reporting (MDR) System. The European Commission has produced Guidelines on a Medical Device Vigilance System that 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 or the European Authorised Representative (EAR) must provide the relevant CA with the name and address for the EAR as well as a description of the devices being placed on the market. Distributors can be designated as manufacturers' authorised representatives, but the commercial implications of such positions need to be carefully considered. The product label or the outer packaging or instructions for use must contain the name and address of the EAR and this is usually done in the IFU. Whilst the MDD Revision does not cover the IVDD it is sensible to follow the revision's direction on only having one EAR, or at least only one per product group.

The manufacturer or the EAR can be the contact person for the competent authorities concerning incidents and related matters. Requests for technical files related to the product and other correspondence can be directed to the EAR if the manufacturer is unavailable.

The Commission requires only a summary technical file, (as described in the MDD section earlier) of this chapter be held by an EAR. It is not necessary to make the full technical file available to the EAR. However, in the case of an incident investigation, a CA has the right to ask for any technical files. In these situations, an EAR may be required to obtain such files from a manufacturer and needs to be able to do so in a timely manner. These may include information

the manufacturer does not want available to a distributor and hence the earlier caution about using a distributor as an EAR.

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

6.3 Labeling

The MDD places strong emphasis on product labeling and instructions for use. The MDD and IVDD do not set out specific language requirements, but allow Member States to include language requirements when enacting Member State legislation to implement the directives. Annex I Essential Requirements Section 8 of the IVDD states:

“The decision whether to translate the instructions for use and the label into one or more languages of the European Union shall be left to the Member States, except that, for devices for self-testing, the instructions for use and the label must include a translation into the official language(s) of the Member State in which the device for self-testing reaches its final user.”

To date, all Member States have demanded the use of their official language(s) for labeling and IFUs, with some exceptions for professional use in a few countries. Manufacturers must provide labeling in the appropriate official language(s) of the Member State for self-test or over-the-counter or lay use devices. From a risk management perspective, manufacturers are encouraged to consider if any other regional and ethnic languages are required to ensure the device can be used safely and effectively all those using the devices.

Annex I Section 8.2 of the IVDD and Annex I Section 13.2 of the MDD indicate that where appropriate, “...the information to be supplied should take the form of symbols. Any symbol and identification colour used must conform to the harmonised standards. In areas for which no standards exist, the symbols and colour used must be described in the documentation supplied with the device.”

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 necessary and expected.

Section 13 of Annex I (ERs) of the MDD specifies the type of information required as does Annex I (ERs), Section 8 of the IVDD. 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.

European Medical Device Labeling – Language Requirements

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

NB: National transpositions vary but the use of the official language(s) of each country is demanded. Some other variations occur with clinical trials and other registration activities that the Commission aims to minimise.

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 the detailed registration of certain higher risk products that differ from country-to-country.

The legal manufacturer not the distributor or agent is fully responsible for all translations and for placing the devices on the market and for meeting national legislation. Distributors and agents are useful for double checking translations but certified translation companies with experience in medical devices are recommended, and demanded, in some cases.

For devices used for self-testing, over-the-counter (OTC) and direct-to-the-consumer (DTC) labeling must be in the official languages and serious consideration should be given to other languages in common use in the country where the devices are placed. This requires a risk based approach. For example in the UK, Welsh and Gaelic are not typically included in IFUs but sometimes Urdu and Hindi are included along with other European languages.

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

Languages

The following includes the EFTA countries of Iceland, Liechtenstein, Norway and Switzerland.

Austria

German: exceptions are 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. One official language is acceptable for professional users but all three are recommended. English is acceptable for professional users if one of the following conditions occurs and is agreed in writing with the user:

- 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).

Bulgaria

Bulgarian: English is acceptable for professional use only. Some software may be in English.

Cyprus

Greek: English is acceptable for professional use only. This is a small country, with around 860,000 people.

Cyprus requires some words such as ‘Lot’, ‘Sterile devices’, ‘Custom Made Device’ and ‘Devices for Performance Evaluation’ to be written in Greek in all cases. Cyprus is in favour of electronic labeling and instructions.

Czech Republic

Czech

Denmark

Danish but “... the Agency can in exceptional cases allow the information to be in one or more of the other official language of the user.” This needs to be carefully checked on a case-by-case basis.

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

Estonia

Estonian: this is a small country, with around 1.3 million people. For IVDs only the information necessary for the safe use of devices has to be in Estonian. Note that more than 25% of the population are Russian and Russian language instructions are worthy of consideration.

Finland

Finnish and Swedish: both languages are recommended for labeling and IFUs to ensure safe use of the device and this is required for self-test devices and patient use devices. Other information supplied must be in Finnish, Swedish or English, unless the information takes the form of generally known directions or warning symbols.

France

French

Germany

German: other official EU languages may be used for non-safety related data.

Greece

Greek: IFUs and package inserts must be in Greek, only information on the label and outer packaging for professional use can be in English. If for patient use information on the label and outer packaging must be in Greek too.

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

Hungary

Hungarian: note that IVD IFUs must be in Hungarian and included with each device.

Iceland (EFTA)

Icelandic is a small country of just over 300,000 people.

Ireland

English

Italy

Italian

Latvia

Latvian: English and German labeling is acceptable for professional use only. This is a small country of around 2.3 million. Note that more than 28% of the population are Russian and Russian language instructions are worthy of consideration.

Liechtenstein (EFTA)

German: however the transposition implies the use of Swiss requirements for language, i.e., German and French and Italian. This is a good approach for Liechtenstein with its small population, i.e. use Swiss labeling. Exceptions can be made if

- The products are intended only for professional use;
- It can be supposed that the professionals understand the English language and agree with it;
- The protection of patients is guaranteed; and

- The translation into German means a disproportionate amount work for the benefits gained.

Liechtenstein has a tiny population of only around 35,500.

Lithuania

Lithuanian: the Lithuania CA has stated electronic IFUs could be used and this could prove useful in the future if followed through into the regulations. Note that around 6% of the population are Polish and around 5% Russian so that Polish and Russian language instructions are worthy of consideration.

Luxembourg

French or German or Luxembourgeois are official languages. English - for professional (doctors not nurses) use only. Luxembourg has a small population of less than 0.5 million.

Malta

Maltese and English are official languages of Malta. All documentation can be in English. Malta will permit e-labeling and IFUs once they are accepted at the European level. Malta has a small population of just over 400,000.

Netherlands, The

Dutch: 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. Continuous verification may be required to ensure this is acceptable.

Norway (EFTA)

Norwegian: for professional use it may be acceptable to use Swedish, Danish or English and the manufacturer should verify the language capability of the user. “Professional Use Only” must be stated in the labelling and is good practice where required elsewhere. Checking with regulatory authorities on a case-by-case basis to be sure of all requirements is recommended.

Poland

Polish: all labels and IFUs need to be in Polish but IFUs in another language can be provided to professional users with their written consent. This is a large country, Polish IFUs are recommended.

Portugal

Portuguese

Romania

Romanian: for the MDD, labels can be in English but the IFU and CE certificates must be in Romanian with translation by a certified translator.

Slovakia

Slovak: some use of Czech in labeling is tolerated, but as this information is based on an informal statement it needs to be checked on a case-by-case basis if required.

Slovenia

Slovenian: Slovenia allows IFUs for professional use products to be in either Slovenian or English. IFUs for self-testing products must be in Slovenian. Slovenia has a small population of just over 2 million.

Spain

Spanish: 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: exceptions from Swedish are, in theory, possible but only for truly exceptional cases that are well justified.

Switzerland (EFTA)

German and French and Italian are the official languages used in Switzerland and all product information must be written in all three. English is acceptable for professional use or custom devices as long as:

- The user has the technical knowledge and the manufacturer has the confirmation from the user that he can understand it;
- The protection of patients, users and third parties is guaranteed;
- The safe and proper use of the device is not jeopardized;
- The use of three languages is too burdensome (can you prove it?); and
- 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. The manufacturers label needs to be more prominent than any other name on the device, i.e. distributor and authorised representative. This is a sensible approach for all such labels.

Candidate Countries for Further Enlargement

Croatia (Hrvatska)

Croatian: English may be permitted for professional use only products but this should be checked on a case-by-case basis.

Former Yugoslav Republic of Macedonia

Macedonian/Albanian: Macedonia has a small population of just over 2 million.

Turkey

Turkish: IFUs need to be in at least two languages: Turkish and either French or German or English.

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 the most useful and important European documents, is contained in Appendix 5: List of Important Documents and Standards of the present guide.

The main home page for medical devices in Europe is found on the Europa web site:

http://ec.europa.eu/consumers/sectors/medical-devices/index_en.htm

The UK's competent authority, the Medicines and Healthcare products Regulatory Agency (MHRA) has many useful documents in English and the home page can be found at

<http://www.mhra.gov.uk/Howweregulate/Devices/index.htm>

Some documents are available free of charge from www.delcan.ec.europa.eu

Copies of relevant ISO and EN standards are also useful. Both ISO and EN standards can be obtained from IHS Energy Canada Ltd through the following website: <http://www.global.ihs.com> or by calling 613 237 4250.

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 1 July 1998, new Medical Devices Regulations (“the Regulations”) came into force, replacing Regulations which 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/text.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. Not sure what to do

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 risk. 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 forms the basis of the Regulations. These requirements 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.

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, or 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. Health Canada updated its “Keyword Index” for medical devices, other than in vitro devices, on 12 September 2006. A draft “Keyword Index” for in vitro devices has also been published. Each of these 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. Each keyword index, along with guidance for the interpretation of the classification rules, can be found on the Health Canada website at

<http://www.hc-sc.gc.ca/dhp-mps/md-im/index-eng.php>

Further guidance may be obtained by viewing the list of Canadian licenced medical devices on the following website: <http://www.mdall.ca>

The classification rules 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 which generally correspond to Canada's four classes, as illustrated in the following table.

<u>Canadian Medical Devices Regulations</u>		<u>European Council Directive 93/42/EEC (MDD)</u>
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

To compare the classifications of other than in vitro devices sold in the Canadian and European markets, one can use the Keyword Index for other than in vitro devices (referred to in this Chapter) with the list of European classified products in Appendix 1 of this Reference Guide.

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.

Health Canada has developed a policy on the use of recognized standards in establishing the safety and effectiveness of medical devices that is similar to the European approach and the references in the MDD to the use of harmonized standards for complying with the essential requirements. This policy can be found on the Health Canada website at the following address: <http://www.hc-sc.gc.ca/dhp-mps/md-im/index-eng.php>

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 information on the device 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 who 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. Health Canada can refuse to issue or can cancel an establishment licence. Establishment licences expire on 31 December of each year.

Health Canada's Health Product's and Food Branch Inspectorate conduct inspections of Establishment licence holders to determine their compliance with the Food and Drugs Act and the Medical Device Regulations.

A current listing of Establishment Licences and guidance on Establishment Licensing can be found on the Health Canada website at

<http://www.hc-sc.gc.ca/dhp-mps/compli-conform/licences/index-eng.php>

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.

These requirements are set out in the Labeling Requirements section of the Regulations (sections 21-23), and include the requirement for the name and address of the manufacturer. 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/index-eng.php>

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 longer of the projected useful life of the device or two years after the date the device is shipped.

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 any inadequacy in the labelling 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
- (c) Could have led to a death or serious deterioration in the health of a patient, user or other person, or could do so were it to recur.

The Mandatory Problem Reporting sections of the Regulations (sections 59 to 61.1) set 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. Mandatory Problem Reporting is also required for custom-made devices and medical devices to be imported or sold for special access (section 77), and for medical devices for investigational testing involving human subjects (section 88).

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/compli-conform/index-eng.php>

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 the results of the recall and the action taken to prevent a recurrence of the problem to Health Canada. The manufacturer and the importer must maintain records related to the recall. Section 65.1 (1) of the *Canadian Medical Devices Regulations* permits the manufacturer to delegate to the importer the responsibility for preparing and submitting, on the manufacturer's behalf, the information and documents referred to above.

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/compli-conform/index-eng.php>

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/index-eng.php>

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-mpps/md-im/index-eng.php>

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

Where a product is manufactured in Canada for export only, and is not intended for consumption in Canada, that product label must show the word “Export” and the manufacturer must have an Export Certificate for that product. 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 Management System Requirements

The quality management 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 management system standard for medical devices: 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 9001:2008 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 management system must satisfy the requirements of CAN/CSA-ISO 13485:2003, excluding design. For class III and IV devices, the quality management system must satisfy the requirements for CAN/CSA-ISO 13485:2003, including design.

It is recommended that the scope of the organization's quality system, as defined in its quality management manual, addresses 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 management system requirements will be required at the time an application is made for a medical device licence. The manufacturer will need to provide a copy of a quality management 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, manufacturers do not need to send copies of the quality management system certificate with the renewal application. However, where a quality management 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/index-eng.php>

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 management system by these accredited registrars. A Health Canada-SCC Management Committee is responsible for managing CMDCAS accreditation-related issues.

Health Canada has 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 Management 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 management system. If the company passes the audit, the registrar recommends that the quality management system be registered to the appropriate ISO standard.

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

- 1) The documentation audit (which may be performed on-site or off-site) during which auditors assess the organization's quality management 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 management 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 management system to ensure continued compliance with the ISO standard. All segments of a company's quality management 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 management system conforms and the registrar will recommend ISO registration;
- 2) A major non-conformance is found and a recommendation for registration cannot be made. A major non-conformance 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 management system. A major non-conformance 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 management 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 met where national or regional regulations require them. For example, an auditor may find that mandatory problem reporting does not satisfy the Canadian Medical Devices Regulations, and will issue a non-conformance against clause 8.5.1 of ISO 13485:2003. That clause requires documented procedures to notify the regulatory authorities of adverse incidents which 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 management system is discovered by auditors; it 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 is 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 \$30,000 and \$35,000 for a quality management system registration, normally valid for three years. 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, 150 Tunney's Pasture Driveway
Postal Locator 0301H1
Ottawa ON
K1A 0K9

Tel.: (613) 957-4786
Fax: (613) 957-7318
Email: mdb_enquiries@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/index-eng.php>

Useful guidance documents can be obtained by visiting the following website:

<http://www.hc-sc.gc.ca/dhp-mps/md-im/applic-demande/guide-ld/index-eng.php>

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 United States (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 by subsequent acts, including 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 and other smaller amendments since then. 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). Aspects of these are described later but they need to be read in detail and monitored for changes. It is important to read these in conjunction with the relevant guidance notes that FDA expects manufacturers to follow, unless there is a good reason for not doing so.

FDA is responsible for regulating firms who manufacture, repackage, relabel and/or import medical devices sold in the US. FDA classifies medical devices that includes In Vitro Diagnostics (IVDs) and enforces the appropriate requirements for premarket notification and postmarketing activities; these include inspection of foreign facilities.

FDA expects all manufacturers to have a quality system appropriate to the product risk profile and size of business. FDA is very supportive of the global use of ISO 13485: 2003 Medical devices - Quality management systems - Requirements for regulatory purposes although it does not recognize it as a consensus standard. ISO 13485: 2003 is consistent with current Good Manufacturing Practice (cGMP) and a comparison of clauses is provided in Appendix 6. GMP design controls are based on ISO 9001:1994 Quality Systems Model for Quality Assurance in Design, Development, Production, Installation, and Servicing, and ISO 13485 Quality Systems Medical Devices Particular Requirements for the Application of ISO 9001, dated April 1996.

Medical devices regulation is controlled by the Center for Devices and Radiological Health (CDRH) and is an excellent source of information that must be used by manufacturers to ensure regulatory compliance is achieved.

Device Advice is considered to be essential reading for all those involved in US regulatory compliance, please see:

www.fda.gov/MedicalDevices/DeviceRegulationandGuidance.

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; it is hard to overstate its importance in these matters.

Each reference provides links to further documents or guidance.

Key topics covered at Device Advice include:

- Overview of Regulations – links to:
 - Radiation-Emitting Electronic Products
 - Classification of Medical Devices
 - Establishment Registration
 - Medical Device Listing
 - Premarket Notification 510(k)
 - Premarket Approval (PMA)
 - Investigational Device Exemption (IDE) for clinical studies
 - Quality System (QS) Regulation
 - Labeling Requirements
 - Medical Device Reporting
- How to Market Your Device
- Postmarket Requirements
- Compliance Activities
- Medical Device Databases
- Guidance Documents
- Standards
- Reprocessing of Single-Use Devices
- Importing and Exporting Devices
- International Information
- Unique Device Identifiers
- IVD Regulatory Assistance

Important Special Note on Web References:

The FDA web site underwent a major change in structure and layout during early June 2009 and old web references in guidance documents may not always work or may not take you to the precise point you need. In this document the web references have been checked but may be subject to change without notice.

Searching on specific document titles or key phrases within the document may assist you with locating them.

There is also a search function available and it 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 in the general FDA A-Z Index (this is not as comprehensive as the previous A-Z provided by CDRH that is no longer available).

The Device Advice home page has a link to the very helpful Division of Small Manufacturers, International and Consumer Assistance (DSMICA) who can also be contacted at 800-638-2041 or 301 796 7100 (fax 301 847 8149) or email FDA at dsmica@fda.hhs.gov. The DSMICA Staff Directory references relevant contacts by the topics for which they are responsible.

Important Special Note on related Centers and Combination Devices:

For some devices containing biological tissue or those used in conjunction with a drug may require reference to one or more of the following:

Center for Biologics Evaluation and Research (CBER): www.fda.gov/BiologicsBloodVaccines

Center for Drug Evaluation and Research (CDER) www.fda.gov/Drugs

There is also an Office for Combination Products (OCP) www.fda.gov/CombinationProducts

OCP provides management of the process required for combination products, including assigning which FDA Center will have primary jurisdiction for review of a combination product. It is important and useful to contact this group early in the regulatory process concerning such combination devices.

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 being the lowest risk, requiring the least stringent controls and the Class III devices being the highest risk, requiring the most stringent controls. It is important to first check in borderline cases if the product is a medical device.

The process for arriving at an FDA device classification is significantly different than 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 28 May 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 but first see Device Advice at

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/ClassifyYourDevice/default.htm>.

To get a definitive determination of the classification of a medical device by the FDA requires the submission of a 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" Address: Document Mail Center – WO66-G609, 10903 New Hampshire Avenue, Silver Spring, MD 20993, USA."

Section 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 has been vital to be clear about the classification at the earliest stage of product development

since the introduction of User Fees with MDUFMA, as the costs (see later section for details) including just applying for different types of premarket review vary enormously. The 513(g) now has a user fee attached to it, as does the annual establishment registration. These are both covered later in this chapter.

The 513(g) user fee for fiscal year 2010 (1 October 2009, to 30 September, 2010) is US\$2,941 and if the applicant qualifies as a small business (\leq US\$100 million sales), US\$1,470.

As a first step, a manufacturer placing any class of device on the market should determine if there is a substantially equivalent legally marketed device that has already been classified. Nearly all Class I devices are premarket notification exempt and so are some Class II devices. If a premarket notification is required and a substantially equivalent legally marketed device (known as a predicate device) found, a premarket 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), to establish if 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 or “risk-based classification.” Please see

www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080195.htm 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 Premarket Approval (PMA) Application to the FDA to enable the FDA to assess the device class (see Premarket 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.

<u>US FDA Device Classifications</u>	<u>Canadian Medical Devices Regulations</u>	<u>European Council Directive 93/42/EEC (MDD)</u>
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; Premarket 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 devices but also require the completion of a PMA [or rarely 510(k)] before a device can be marketed. Device Advice provides useful information on PMAs at [Premarket Approval \(PMA\)](#). “Premarket 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 premarket 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 itself!

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 do the following:

- register each manufacturing establishment (21 CFR Part 807.20);
- list marketed medical devices;
- manufacture devices in accordance with the GMP regulation (21 CFR 820);
- label devices appropriately (21 CFR 801 or 809); and
- submit a premarket notification 510(k). [Most Class I devices are exempt and Class III devices usually require a premarket approval (PMA)].

The general controls include provisions that relate to product that does not conform with specifications and remedies including adulteration; misbranding; banning of devices; notification, including repair, replacement, or refund; records and reports; and restrictions.

For more on General and Special Controls please see:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/GeneralandSpecialControls/default.htm>

Please also see the requirement for Unique Device Identifiers that medical devices marketed in the US should now consider. This can take several forms including bar coding:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/UniqueDeviceIdentifiers/default.htm>

According to Jay Crowley, the key FDA contact on this subject, the draft regulation governing the use of unique device identifiers (UDIs) on medical products is on schedule to be published by the middle of 2010, with the final regulation targeted for 2011. At the time of writing, it is estimated that the highest risk class III devices will need to conform to the new UDI regulations by the end of 2012, followed by class II devices in 2015 and class I devices in 2016. The purpose of UDIs is to create a system for tracking a medical device through the distribution chain and in use. The Global Harmonization Task Force (GHTF) has established an ad hoc UDI working group and this group is working closely with the FDA on recommendations for a global UDI model.

1.2.1 Establishment Registration

An owner or operator of an establishment, including foreign establishments, 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. (See FDAMA Section 417 and

www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/RegistrationandListing/ for Establishment Registration, Device Listing and US Agent).

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.

The purpose of establishment registration is to enable FDA to know where the establishment is, who owns and operates it and with whom to communicate about it.

Establishment registration is not an approval of that establishment, nor is it an approval of any products produced by that establishment. “Unless exempt, premarketing clearance or approval is required before a device can be placed into commercial distribution in the U.S.”

Since 1 October, 2007, all establishment registrations have to be submitted electronically, using the FDA’s Unified Registration and Listing System (FURLS), unless a waiver has been granted by the FDA.

Comprehensive details are provided at the Device Advice section including how to pay, who has to register and when to register. There is a need to have an account ID and password in FURLS in order to submit a registration, so this has to be set up first, if not already completed.

It is recommended by FDA that the email address provided to FDA is for the designated Official Correspondent. This makes sense, as the Official Correspondent is the person designated by the owner/operator to be responsible for

- The annual registration of the establishment.
- Contact with FDA for establishment registration and medical device listing issues.
- Maintenance and submission of a current list of officers and directors to FDA upon request.
- The receipt of pertinent correspondence from FDA directed to and involving the owner/operator and/or any of the firm's establishments.

There may be a need to create sub-accounts for the Official Correspondent for each registered establishment.

Foreign companies have to inform FDA of who their US Agent is prior to exporting devices to the US.

The establishment registration user fee for fiscal year 2010 (1 October 2009, to 30 September

2010) is US\$2,008 and is the same for businesses of all sizes. Annual registration between the October 1st and December 31st each year is required. Fees up to FY 2012 are available at

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/RegistrationandListing/default.htm>

Once registration has been completed, FDA will send an email notifying the official correspondent of the Owner Operator number to be used in any correspondence with FDA.

1.2.1.1 United States Agent for Foreign Establishments (US Agent)

The United States Agent for Foreign Establishments (US Agent) became effective 11 February 2002. Please see:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/RegistrationandListing/ucm053196.htm>

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.

1.2.2 Device Listing

The initial device listing needs to follow on from the establishment registration and both are relatively simple administrative tasks for most companies and products.

As with establishment registrations, device listings have to be submitted electronically using the FDA's Unified Registration and Listing System (FURLS), unless a waiver has been granted by FDA. Comprehensive details are provided at the device advice section including what a medical device listing is, who must list, when to list and how to list. There is no fee to pay; this is taken

into account in the establishment registration. FDA expect the initial device listing to be completed as part of the establishment registration and both updated as changes occur, or verified at least annually between 1 October and 31 December.

A listing of a medical device is not an approval of the establishment or a device by FDA. “Unless exempt, premarketing clearance or approval is required before a device can be placed into commercial distribution in the U.S.”

Device listing provides FDA with identification of the generic categories of devices that an establishment is manufacturing or marketing. Devices are classified under Title 21 of the CFRs Parts 862-892 or FDA assigned name. These have product codes associated with them and a particular regulation may have several product codes for different products. The product code is needed and is useful for searching FDA databases. Please see:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/RegistrationandListing/default.htm>

1.2.3 Premarket Notification - 510(k)

When marketing a device subject to premarket 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 Device Advice provides extensive detailed guidance: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/default.htm>

1.2.3.1 510(k) Clinical Trial Certification

Since 26 December 2007, all 510(k) submissions that require clinical data must include form FDA-3674 available from:

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048364.pdf>

“If your 510(k) includes data from a clinical trial, you must determine if your study is applicable for entry into the clinical trial registry data bank at ClinicalTrials.gov. Based on this determination, check box 9.B. or 9.C., and complete the applicable sections of the form. An applicable device clinical trial is a prospective clinical study of health outcomes comparing an intervention with a device against a control in human subjects (other than a small clinical trial to determine the feasibility of a device, or a clinical trial to test prototype devices where the primary outcome measure relates to feasibility and not to health outcomes). See [Title VIII - Clinical Trial Databases](#). Currently, FDA is reviewing the legislation and developing guidance on which clinical trials meet the definition of "applicable" trials and are required to report to ClinicalTrials.gov. Until FDA issues this guidance, 510(k) submitters are responsible for determining whether their studies meet the definition of an applicable trial and, therefore, are subject to reporting requirements.

Information on how to register your clinical trial(s) in the ClinicalTrials.gov data bank is available on the National Library of Medicine (NLM) [Protocol Registration System](#) (PRS) website.”

Applicable trials are essentially those relied upon for the submission. The form and many others that may be required are available from:

<http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/default.htm>.

For more on the trial registration process please see: www.clinicaltrials.gov/ct2/info/about.

1.2.3.2 510(k) Use of Standards – Form 3654

Since 2 January 2008, all 510(k) submissions (Traditional, Abbreviated or Special) that reference

“...a national or international standard should include a completed Standards Data Form for 510(k)s (FDA Form #3654, Form Approved OMB #0910-0120) as part of their 510(k).”

The form is available from:

<http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/default.htm>

There is further guidance in Recognition and Use of Consensus Standards available from:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Standards/default.htm>

1.2.3.3 510(k) Review Fees

The Medical Device User Fee and Modernization Act (MDUFMA) of 2002 introduced User Fees for 510(k) and PMA applications (please see later section on MDUFMA) please see:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/MedicalDeviceUserFeeandModernizationActMDUFMA/default.htm>

Foreign based firms can now qualify for the ‘Small Business Fee’ scale. This means for FY2010 (1 October 2009, to 30 September 2010) applicants will have to pay: US\$4,007 or if a small business US\$2,004. Canadian firms should refer to Appendix 7 of this guide for information on the Small Business Discount.

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; the information and is taken directly from Device Advice at:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/ucm134566.htm>

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 and Quality System (QS) 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 were 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 legal status whereas the QSR Manual is guidance. The manual is very readable and includes many useful examples of what is required. It is considered essential reading for all those interested in the detailed quality system requirements. Please see:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/QualitySystemsRegulations/MedicalDeviceQualitySystemsManual/default.htm>

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

The ‘Guide to Inspections of Quality Systems,’ (QSIT) published in August 1999, is an important document that informs manufacturers how they are likely to be inspected in a routine audit of their facilities. It has five main sections: management controls, design controls, corrective and preventive actions (CAPA), production and process controls (P&PC) and sampling plans. Please see:

<http://www.fda.gov/ICECI/Inspections/InspectionGuides/ucm074883.htm>

Please see also the Quality System Regulation section given later in this document that provides more useful information on FDA and quality systems.

The Quality System (QS) Regulation / Medical Device Good Manufacturing Practices guidance is available at Device Advice at:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/QualitySystemsRegulations/default.htm>

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 nonsignificant risk device, submission to the FDA is not required, but IRB approval is required.

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 details please see:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/default.htm>

This site 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.

Quality System Requirements For Medical Devices

- 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/cfcr/CFRSearch.cfm?CFRPart=58>)

1.4 Premarket Approval

Premarket 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” refer to devices placed on the market prior to 28 May 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” refer to devices marketed on or after 28 May 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, Device Advice provides a useful summary of regulatory and quality requirements. Please see:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/default.htm>

The main CFRs that apply are:

[21 CFR 814 Premarket Approvals of Medical Devices](#)

[21 CFR 54 Financial Disclosures 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).
4. Final deliberations, documentation, and notification of the FDA decision.

1.4.1 Clinical Trial Certification

Since 26 December 2007, all PMA submissions must include form FDA-3674 available from: <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048364.pdf>

“If your PMA includes data from a clinical trial, you must determine if your study is applicable for entry into the clinical trial registry data bank at ClinicalTrials.gov. Based on this determination, check box 9.B. or 9.C., and complete the applicable sections of the form. An applicable device clinical trial is a prospective clinical study of health outcomes comparing an intervention with a device against a control in human subjects (other than a small clinical trial to determine the feasibility of a device, or a clinical trial to test prototype devices where the primary outcome measure relates to feasibility and not to health outcomes).

See [Title VIII - Clinical Trial Databases](#). Currently, FDA is reviewing the legislation and developing guidance on which clinical trials meet the definition of "applicable" trials and are required to report to ClinicalTrials.gov. Until FDA issues this guidance, the PMA sponsor is responsible for determining whether its studies meet the definition of an applicable trial and, therefore, are subject to reporting requirements.

Information on how to register your clinical trial(s) in the ClinicalTrials.gov data bank is available on the National Library of Medicine (NLM) [Protocol Registration System](#) (PRS) website.”

The form and many others that may be required are available from: <http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/default.htm>.

Canadian firms should refer to Appendix 7 of this guide for information on the Small Business Discount.

For more on the trial registration process please see: www.clinicaltrials.gov/ct2/info/about and follow the links.

1.4.2 PMA Review Fees

The Medical Device User Fee and Modernization Act (MDUFMA) of 2002 introduced User Fees for 510(k) and PMA applications (please see later section on MDUFMA) and foreign based firms can now qualify for the ‘Small Business Fee’ scale. This means for FY2010 (1 October 2009 to 30 September 2010) applicants will have to pay upfront: US\$217,787 or if a small business \$54,447. Please see:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/RemarketSubmissions/PremarketApprovalPMA/ucm048161.htm>

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.” FY 2010 fees for changes to PMAs are expensive:

Quality System Requirements For Medical Devices

180-day Supplement fee at US\$32,668 or US\$8,167 if a small business and Real-Time Supplement at US\$15,245 or US\$3,811 if a small business;

30-day Notice US\$3,485 or US\$1,742 if a small business;

Annual Fee for Periodic Reporting US\$7,623 and if a small business US\$1,906;

The fee is waived for the first premarket application from small firms with gross receipts or sales <\$30 million.

The definitions concerning what the listed changes are and related guidance is available from:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089726.htm>

The following exemptions or waivers apply and the information is taken directly from Device Advice:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/ucm048161.htm>

Exemptions and Waivers

The following types of applications require no fee:

- Special PMA Supplements - Changes Being Affected
- PMA Manufacturing Site Change Supplements
- 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 premarket application (PMA, PDP, BLA, or premarket 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 premarket application.
Any application from a State or Federal Government entity.	Exempt from any fee unless the device is to be distributed commercially.

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 28 May 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 21 November 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 from Dr. Bruce Burlington, then Director of CDRH.

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

- user fees for premarket reviews;
- establishment inspections may be conducted by accredited persons (third-parties); and
- new regulatory requirements for reprocessed single-use devices.

For more detail on MDUFMA please see:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/MedicalDeviceUserFeeandModernizationActMDUFMA/default.htm>

This site includes Frequently Asked Questions (FAQs).

The SMDA of 1990, sets out a number of provisions for medical devices, some of which have since been altered by FDAMA and MDUFMA. These are briefly described next.

1.5.1 Medical Device Reporting (MDR)

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 modified requirements on the frequency of reporting from semi-annual to annual. The report is now due on January 1st 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.

Amendments to the MDR Regulation to Implement FDAMA Changes

Please see:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/ReportingAdverseEvents/ucm127985.htm>

“The reporting changes are:

1. Medical device manufacturers, importers, and distributors are no longer required to submit an annual certification statement.
2. Domestic distributors no longer have to submit MDR reports, but they must continue to maintain records of adverse events.
3. Importers continue to be subject to the remaining requirements of the MDR regulation, 21 CFR 803.

4. User facilities now submit a report annually instead of semi-annually.

The MDR Rule changes became effective 27 March 2000.”

General Guidance

To understand current FDA requirements better, refer to the main page at FDA for information on the important topic of adverse incident report, known by FDA as Medical Device Reporting (MDR) at:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/ReportingAdverseEvents/default.htm>

MDR is FDA’s mechanism for receiving significant “medical device adverse events from manufacturers, importers and user facilities, so they can be detected and corrected quickly.”

Health professionals and consumers, i.e. the public are directed to use the MEDWATCH program to report significant adverse events or problems with medical products. This is well supported on the web at www.fda.gov/medwatch/

It is important that all those delivering healthcare using medical devices know what is important to report, and who to report it to in the event of an adverse incident. Distributors who become aware of an adverse incident need to work closely with the manufacturer to ensure these incidents are reported in a timely manner. There are expected timescales for reporting incidents that range from within 5 days to 30 days, depending upon the actions required.

Databases on general information, MAUDE and MDR are available, as is guidance, user facility reporting bulletins and Federal Register Notices. There are links to Medical Device Tracking and Post market Surveillance that are important topics in their own right.

The Manufacturer and User Facility Device Experience (MAUDE) database “...consists of voluntary reports since June 1993, user facility reports since 1991, distributor reports since 1993, and manufacturer reports since August 1996. MAUDE may not include reports made according to exemptions, variances, or alternative reporting requirements granted under 21 CFR 803.19.2.”

The MDR database link provides information from CDRH’s former database, the device experience network (DEN). “The reports include mandatory manufacturer reports on devices which may have malfunctioned or caused a death or serious injury. These reports were received under both the mandatory Medical Device Reporting Program (MDR) from 1984 - 1996, and voluntary reports up to June 1993. There are over 600,000 reports.”

How to Report a Problem

Some history of the MDR Regulation is provided by FDA since there are a lot of documents and references that have been amended by various acts. This is covered at the FDA's MDR pages under How to Report a Problem and includes the history and updates. Please see:

<http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm>

Manufacturers should note the FDA contact details at:

<http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/ucm124082.htm>

Electronic MDR (eMDR)

This is currently a hot topic as FDA has proposed mandatory eMDR; please see the 20 August 2009, press release at

<http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm179596.htm>

There is no specific date yet, but manufacturers would be well advised to explore how this might affect their quality systems and document control as soon as possible. For general information about current eMDR please see:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/ReportingAdverseEvents/eMDR-ElectronicMedicalDeviceReporting/default.htm>

Reports can be submitted on appropriate written forms or can be completed electronically on-line. The electronic MDR (eMDR) utilizes the FDA Gateway, the agency's entry point for all electronic submissions, and manufacturers can register to use this for eMDR. There are two systems available for submitting reports, one for low volume users and an alternative for high volume reporters.

CDRH eSubmitter (CeSub) is for low volume reporting (less than 50 per month), one at a time; and FDA provides free downloadable software for this purpose.

Health Level 7 (HL7) Individual Case Safety Report (ICSR) is for high volume (more than 50 per month).

1.5.2 Medical Device Tracking Requirements

Manufacturers must have a system in the form of a standard operating procedure for tracking devices, "whose failure 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 are life-sustaining or life-supporting devices used outside of a device user facility." Active implantable devices like pace makers or defibrillators are examples of products subject to this regulation.

FDAMA allows FDA to order manufacturers to initiate patient tracking of some devices down to the patient level, where considered necessary or appropriate.

Examples of the types of devices FDA has ordered to be tracked can be found in the Guidance on Medical Device Tracking. For a list of devices subject to the tracking requirements and useful guidance information please see:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/MedicalDeviceTracking/default.htm>

FDAMA allows “patients receiving a tracked device to refuse to release, or refuse permission to release, their name, address, social security number, or other identifying information for the purpose of 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 FD&C Act that may present a risk to health. The requirement still applies to manufacturers and importers.

For more on this topic please see:

[Recalls, Corrections and Removals \(Devices\)](#)

1.5.4 Post market Surveillance

The manufacturer is required to undertake postmarket surveillance on certain products that have been designated by the FDA as requiring postmarket 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 postmarket surveillance activities are required under the EU MDD and Canada’s Regulations.

FDA has a web section for post market surveillance that has further links to comprehensive information:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/PostmarketSurveillance/default.htm>

FDA has the authority to order postmarket surveillance of any Class II or Class III medical device that meets any of the following criteria that are the same as those for device tracking, i.e.:

- Failure of the device would be reasonably likely to have serious adverse health consequences;
- The device is intended to be implanted in the human body for more than 1 year; or
- The device is intended to be used to support or sustain life and to be used outside a user facility.

FDA defines postmarket surveillance as “... the active, systematic, scientifically valid collection, analysis, and interpretation of data or other information about a marketed device. The data can reveal unforeseen adverse events, the actual rate of anticipated adverse events, or other information necessary to protect the public health. Title 21 CFR 822, Post market Surveillance, provides procedures and requirements for post market surveillance.”

This definition is very different to the general surveillance of a market or product used in the EU medical device regulatory system.

Manufacturers of implanted devices know that this is a requirement and plan accordingly. Sometimes postmarket surveillance is part of an order sent to a manufacturer as part of a premarket clearance, or more typically premarket approval, or if there is a need to answer some concern that requires such surveillance.

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/MedicalDevices/DeviceRegulationandGuidance/Overview/MedicalDeviceProvisionsofFDAModernizationAct/default.htm>

This includes a link to an overview, 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 premarket 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 taken from:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094526.htm>

Please also see more on the least burdensome approach at

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/MedicalDeviceProvisionsofFDAModernizationAct/ucm136685.htm>

“FDAMA did not change the statutory threshold for premarket 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.
- All reasonable measures should be used to reduce review times and render regulatory decisions within statutory timeframes.

The above is quoted from:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm085994.htm>

All of FDAMA is potentially of relevance and to go through every point would only duplicate the FDA web site. It is important to visit, and keep visiting this site to keep up-to-date. Below, is a sample from FDAMA to encourage readers to further examine this helpful legislation. Samples are taken directly from Device Advice.

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 the 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 forward for recognition by FDA and used in PMA or 510(k) applications.

Section 206 - Premarket 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 Premarket 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 postmarket 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 postmarket 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

It 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 premarket 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

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/MedicalDeviceUserFeeandModernizationActMDUFMA/default.htm>

This is worth reading to ensure that 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:
 - Postmarket 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

Third-Party Inspections

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 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 provided 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.”

“Electronic Labeling”

§ 206 of MDUFMA and § 2(b) (2) (B) of MDTCA amend section 502(f) of the FD&C Act to permit device labeling to be provided "solely by electronic means" for: --

- Prescription devices intended for use by a health care professional, regardless of the setting in which the device is used.
- Prescription devices intended for use in a health care facility.
- In vitro diagnostic devices intended for use by a health care professional, regardless of the setting in which the device is used.
- In vitro diagnostic devices intended for use in a blood establishment.

The electronic labeling must comply with all other requirements of the FD&C Act; and a manufacturer who uses electronic labeling must "promptly" provide a paper copy of the labeling upon request, at no additional charge.

The following FDA table summarizes the law as it now stands.

When May Electronic Labeling Be Used?				
Setting Where Device is Intended to be Used	Prescription Devices		<i>In Vitro</i> Diagnostic Devices	
	Intended to be Used by a Health Care Professional	All Other Users	Intended to be Used by a Health Care Professional	All Other Users
Health Care Facility	✓	✓	✓	✗ ¹
Blood Establishment	✓	✗	✓	✓
All Other Settings	✓	✗	✓	✗

✓ = Permitted ✗ = Not Permitted

¹ If the in vitro diagnostic device is also a prescription device intended to be used in a health care facility, electronic labeling may be used.”

The table is taken directly from:

<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/Overview/MedicalDeviceUserFeeandModernizationActMDUFMA/ucm109131.pdf>

This link also provides a Summary of the Medical Devices Technical Corrections Act (MDTCA) of November 2004.

For more on electronic labeling and related issues please see:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/MedicalDeviceUserFeeandModernizationActMDUFMA/ucm109200.htm>

1.5.7 Reprocessing of Single-Use Devices

The home page of this important topic is found at

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/ReprocessingofSingle-UseDevices/default.htm>

This is a serious public health issue, as the reprocessing of single-use devices that are not validated can potentially put patients at risk.

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

1.5.8 Identification of Device Manufacturer

“MDUFMA § 301(a) adds a 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) went into effect 26 October 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.”

Please see the earlier section 1.2 General Controls on UDI.

1.5.9 Food and Drug Administration Amendments Act (FDAAA) of 2007

<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCA/ct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/default.htm>

“On September 27, 2007, President George W. Bush signed into law H.R. 3580, the Food and Drug Administration Amendments Act of 2007, with HHS Secretary Michael Leavitt, FDA Commissioner Andrew von Eschenbach, and Rep. Joe Barton of Texas in the Oval Office. This new law represents a very significant addition to FDA authority. Among the many components of the law, the Prescription Drug User Fee Act (PDUFA) and the Medical Device User Fee and Modernization Act (MDUFMA) have been reauthorized and expanded. These programs will ensure that FDA staff have staff has the additional resources needed to conduct the complex and comprehensive reviews necessary to new drugs and devices.”

Quality System Requirements For Medical Devices

This amendment:

- introduced the Electronic Registration and Listing requirements discussed earlier;
- introduced unique device identification system mentioned earlier;
- provided revised guidance concerning facility inspection by Accredited Persons;
- promoted the development of pediatric devices; and
- reauthorized Medical Device User Fees from 2008 to 2012.

2 Quality System Regulation – further discussion

This regulation is built on the Good Manufacturing Practice (GMP) Regulation as discussed earlier in section 1.2.4 of this Chapter. The full QS Regulation can be accessed in the FDA Code of Federal Regulations 21 CFR 820:

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=820&showFR=1>

These regulations are based on the ISO 9001: 1994 quality management system standard and early versions of ISO 13485. 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 aim, championed by the Global Harmonization Task Force (GHTF), was to create a global quality management standard for medical devices and ensure it was compatible with FDA requirements.

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 current GMP is often referred to as cGMP to denote the latest and current version of GMP and QSR regulation.

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 1 June 1997.

The earlier GMP section 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.

The simple summary is that FDA now considers that ISO 13485: 2003 Medical devices - Quality management systems - Requirements for regulatory purposes meets the core requirements of cGMP when appropriately implemented.

Please note the Quality System link at Device Advice explains the relationship between ISO 9001: 2000 and FDA Quality System Regulation in a short document:

<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/QualitySystemsRegulations/UCM134625.pdf>

There is also a comparison between the 1996, QS Regulation, original 1978 GMP and ISO 9001/ISO13485 (1996) approaches that provides part of an audit trail of how the GMP was addressed in ISO 13485. Although dated, it is still a useful reference. It is available from:

<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM072749.pdf>

These documents complement the comparisons listed within EN ISO 13485: 2003 and PD ISO/TR 14969: 2004 discussed in the next section of this guide. 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 on which any medical device manufacturer can base a globally compliant quality system.

2.1 Evolution of ISO 13485

The way that ISO 13485: 2003 Medical devices - Quality management systems - Requirements for regulatory purposes, has risen to become recognized as a global standard is important to understand and is complemented by ISO/TR 14969: 2004 Medical devices - Quality management systems - Guidance on the application of ISO 13485: 2003.

Please note:

- EN ISO 13485: 2003 replaced the two earlier standards: EN ISO 13485: 2000 and EN ISO 13488: 2000 in Europe. These replaced the 1996 versions.
- The earlier standards EN ISO 13485: 2000 and EN ISO 13488: 2000 ceased to provide presumption of conformity with relevant Essential Requirements of the MDD on 31 July 2006, at the end of the agreed transition period.

It is noted that 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 very similar, although the changes have moved the standard to be in closer compliance with US FDA QSR requirements provided the system is rigorously implemented.

- ISO 13485: 2003 became a harmonized standard for all the European medical device directives on 2 April 2004.
- ISO/TR 14969: 2004 Medical devices - Quality management systems - Guidance on the application of ISO 13485: 2003 is not a harmonized standard for the medical device directives.

There is no direct equivalent to EN ISO 13488: 2000. EN ISO 13485: 2000 does not have a design control section. As with ISO 9001: 2000 the manufacturer has to actively justify opting out of design controls; this is now termed “product realization” in ISO 13485: 2003.

EN ISO 13485: 2003 has two very helpful annexes that are considered particularly useful in understanding the standards’ evolution. They compare obsolete standards with newer ones:

- 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 for a complete understanding of the evolutionary changes:

- 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 and as EN ISO 13485: 2003 is both the European harmonized standard and has become the global standard, developed with the full assistance of the Global Harmonization Task Force (GHTF) that includes the USA; it makes sense to use it!

Please see Appendix 6: Comparison Table of ISO 13485: 2003 and FDA’s Quality System Regulation; this provides a side-by-side comparison of clauses to assist manufacturers in understanding how one quality system can address both ISO 13485 and the QS Regulations.

2.1.1 Special Note on ISO 9001: 2008

ISO 9001: 2008 Quality management systems – Requirements is in use but does not change the comments or approach indicated for ISO 13485: 2003; indeed, ISO 9001: 2008 has moved closer to ISO13485 in a number of sections. The final links with “Quality Assurance” have been removed and details of changes are given in Annex B of ISO 9001: 2008. The word risk appears in the introduction in regard to the business environment and organization. Risk is a concept medical device manufacturers are familiar with, from a product angle but it is worthy of extending it into the business environment too. ISO 9001 supports consideration of other

management systems and in the 2008 version Annex A indicates the correspondence with ISO 14001: 2004 Environmental management systems - Requirements with guidance for use.

Outsourcing has notes concerning the need for control and conformity to statutory and regulatory requirements, as required by ISO 13485: 2003. The type and extent of control to be applied to outsourced processes needs to be considered in ISO 9001: 2008. This outsourcing requirement is not included in ISO 13485: 2003, although it is implied by the purchasing requirements. Such requirements are expected by FDA and the medical devices directives, especially since the revision of the Active Implantable Medical Devices Directive (90/385/EEC, AIMDD) and Medical Devices Directive (93/42/EEC, MDD) by Directive 2007/47/EC.

The control of records has moved closer to the wording of ISO 13485 but it should be noted that ISO 9001: 2008 makes it clear that the management representative is expected to be a member of the organization's management team.

Other changes bring ISO 9001 closer to ISO 13485 although detailed wording differs, such as the inclusion of information systems in infrastructure and the added note on software in section 7.6 Control of monitoring and measuring. It is noted that Sections of the standard dealing with corrective action and preventive action include a focus on effectiveness within the review required, as demanded by ISO 13485: 2003.

It is still possible for a medical device manufacturer to comply with both ISO 9001 and ISO 13485 if desired. Clearly the customer satisfaction and continuous improvement requirements are not a part of ISO 13485 and FDA requirements but maintaining the effectiveness of the system is. The focus of medical device quality systems is to meet both customer requirements and comply with regulations in the jurisdictions where the organization operates.

2.1.2 Special Note on 21 CFR Part 11 Electronic Records; Electronic Signatures

In the US, electronic processing of information in the manufacture and use of medical devices is subject to regulation under 21CFR Part 11 Electronic Records: Electronic Signatures and guidance is available in various documents from the following web location:

www.fda.gov/RegulatoryInformation/Guidances/ucm125067.htm

This provides guidance on the scope and application of the requirements. Electronic records and signatures are important topics for secure and reliable implementation of information and communication technology (ICT). Electronic records and signatures need to be protected and maintained electronically.

This is a huge topic.

It is important to consider how to comply and specialist advice is likely to be necessary.

2.1.3 Global Harmonization Task Force

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.

FDA is a major influence within the Global Harmonization Task Force (GHTF); it is a voluntary organization with many of the best persons from regulators and industry contributing to its content. Please visit www.ghtf.org

“The purpose of the GHTF is to encourage convergence in regulatory practices related to ensuring the safety, effectiveness / performance and quality of medical devices, promoting technological innovation and facilitating international trade. The primary way in which this purpose is accomplished is via the publication and dissemination of harmonized documents on basic regulatory practices. These documents, which are developed by five different GHTF Study Groups, provide a model for the regulation of medical devices that can then be adopted or implemented by national regulatory authorities.”

The five main study groups in the GHTF are:

- Study Group 1: *Premarket Evaluation;*
- Study Group 2: *Postmarket Surveillance/Vigilance;*
- Study Group 3: *Quality Systems;*
- Study Group 4: *Auditing; and*
- Study Group 5: *Clinical Safety/Performance.*

GHTF promotes convergence of regulatory requirements and this includes premarket submissions and innovative programs like the “STED” initiative. The “Summary Technical Documentation for Demonstrating Conformity to the Essential Principles of Safety and Performance of Medical Devices (STED) can be found amongst the final documents produced by Study Group 1. FDA recognizes the STED approach for some medical devices. The GHTF quality systems approach and other available documents provide international manufacturers with useful guidance that will assist them in creating systems for meeting global medical device quality system requirements.

2.2 FDA Facility Inspections

The FDA does not require a manufacturer to register a quality system (a requirement of some European conformity assessment procedures). The FDA rigorously inspects 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 findings on 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 - this 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.

The Medical Device Quality Systems Manual: A Small Entity Compliance Guide, First Edition details the requirements of the QS regulation and provides detailed guidance on how to prepare for an FDA Inspection in Chapter 18.

The Medical Device Quality Systems Manual: A Small Entity Compliance Guide:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/QualitySystemsRegulations/MedicalDeviceQualitySystemsManual/default.htm>

Chapter 18 FDA Inspections:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/QualitySystemsRegulations/MedicalDeviceQualitySystemsManual/ucm122743.htm>

The Investigations Operations Manual (IOM) Subchapter 5.6 Devices is the FDA field and CDRH staff manual for inspections. This is an easy to read document with useful insights.

Please see: <http://www.fda.gov/ICECI/Inspections/IOM/ucm122534.htm>

The medical device inspection and enforcement activities are described in detail in the very useful and insightful Compliance Program 7382.845, Inspection of Medical Device Manufacturers. It is comprehensive and important for those managing facilities subject to FDA inspections and useful for top management to have read it at least once. It is recommended for quality managers and regulatory affairs professionals. Please see:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm072753.htm>

2.2.1 Quality System Inspection Technique

The Quality System Inspection Technique (QSIT) Handbook details how a routine inspection will be undertaken and is very similar to the approach taken by European auditors that is based on international standards. This should be read by all management. This and much other useful guidance is available from the FDA's Quality System Inspection Guides Section:

<http://www.fda.gov/ICECI/Inspections/InspectionGuides/ucm074883.htm>

The principle areas inspected by FDA and why, can be summarized as:

Management Controls (responsibility)

- Do you have adequate resources?

Design Controls (ISO 9001: 1994 and now ISO 13485: 2003)

- Do you design for validation?

Corrective Action & Preventive Action (always examined)

- Is this evident in every action?

Production and Process Controls (are you in demonstrable control)

- Do you know what you have made?

QSIT requires FDA to use scientifically based sampling plans when examining records.

3 Information Sources

The most useful FDA resource for all manufacturers is Device Advice and all the documents it references, as repeatedly mentioned in this guide, at

www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/default.htm

The Device Advice home page has a link for the very helpful Division of Small Manufacturers, International and Consumer Assistance (DSMICA) who can also be contacted at 800-638-2041 or 301 796 7100 (fax 301 847 8149) or email FDA at dsmica@fda.hhs.gov. The DSMICA Staff Directory identifies relevant contacts by the topics for which they are responsible.

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 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 is now possible by approved bodies 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 is recommended to contact Health Canada to determine which Registrars are accredited.
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. 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 the following:
 - Postmarket 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 for 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)

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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

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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

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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 your 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. If it is a CE Mark audit, does your company work with a Canadian affiliate?
6. 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?
7. Do you offer information sessions with clients?
8. What is the application process?
9. What are your criteria for recommending a client for registration? Define terms such as, major and minor nonconformances.
10. What is your reassessment or on-going surveillance process? Are there any particular standards that are subject to review at every reassessment?
11. How long are the CE Mark and other certifications valid?
12. How do you assure continuity between the initial assessment and the surveillance assessment?
13. What fees, expenses or other charges are typically associated with registration and surveillance visits?
14. What are your required lead- times for the various stages in the registration and surveillance process?
15. 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

- Indicate that 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 the business, timing, cost, receiving additional registration certificates and proximity to the 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 – Technical Documentation

All medical devices are required to be supported, in their CE marking, by technical documentation held in a “Technical File”. A “Design Dossier” is the most comprehensive form of this required for Class III devices. Not every item below will apply to every device but it is a useful checklist.

Please see the earlier MDD Technical Documentation section that includes a list of what is expected in Part A of the Technical File. The Part B includes more detailed technical documentation for the risk assessment process, information concerning the quality manual, plans, product design, processes, standards applied, etc.

The core elements include a description of the device; its intended use and classification; proof of compliance with all relevant Essential Requirements (ERs) of applicable directives; risk assessment to EN 14971; clinical data as per Annex X of the MDD or performance evaluation for IVDs; and information supplied such as labelling and instructions for use.

The following is based on the MDD (Annex I, Annex II 3.2 & 4.2; and Annex VII), previous documents published by Eucomed (but which are no longer available) and NB-MED/2.5.1/Rec5 Technical Documentation and should be included where applicable:

1. The name and address of the manufacturer.
2. A general description of the device, including any variants planned.
3. A description of the intended use and operation of the device.
4. A classification rationale under the relevant directive to which the CE marking is applied.
5. A general description of the design, manufacture, and performance of the device including documents needed to assess whether the device conforms to the Essential Requirements (ERs) of the MDD; an Essential Requirements Assessment Checklist listing each ER and stating whether it is applicable to the device in question or not; standards or other documents used and the basis for claiming compliance. Including comments and location of relevant documents has become standard practice (although this is not mandatory) and it is very useful for all involved.
6. For products incorporating a medicinal substance or blood derivative substance, the purpose of this substance and mode of action must be made clear in a statement. The Notified Body (NB) will also need to obtain an opinion on the ancillary substance that should be part of the Design Dossier. Annex I 7.4 of the MDD provides more details about this.
7. Materials that are classified as carcinogenic, mutagenic or toxic to reproduction, such as phthalates will require appropriate

labeling and justification for their use when used in the treatment of children or pregnant or nursing women.

8. For products incorporating non-viable materials of animal origin need to address the additional requirements of Animal Tissues Directive (2003/32/EC) and relevant standards, where applicable. See Annex I 8.2 of the MDD.
9. 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.
10. List A IVDs need to take into account the additional requirements of the Common Technical Specification (2009/108/EC).
11. All manufacturers need to consider which of the environmental directives, such as the Packaging and Packaging Waste Directive (PPW, 94/62/EC) apply and to ensure that their requirements are met too.
12. Products may also be subject to the Personal Protective Equipment (PPE, 89/686/EEC) or Machinery (2006/42/EC) Directives and any requirements need to be determined and included in the technical documentation.
13. Any other directives that are applicable should be addressed in the technical documentation.
14. Reference should be made to the quality system procedures / quality system, including the quality manual. Any subcontracting or third party provision of design, manufacture, and/or final inspection and testing of the products or elements of products requires proof that appropriate controls are in place; and it is recommended such relationships be the subject of commercial contracts.
15. The detailed design specifications, including the standards which have been applied and the results of the risk assessment (to EN 14971). A description of the solutions adopted to fulfill the Essential Requirements (ERs) which apply to the devices if the standards referred to in Article 5 of the MDD (i.e. harmonised standards with a presumption of conformity) are not applied in full. These include materials used, design drawings, components, subassemblies, packaging details, product test reports and methods of manufacture.
16. Any relevant certifications or approvals such as design examination certificates.
17. The techniques used to control and verify/validate the design processes.
18. A description of how sterilization is performed and validated, if applicable.
19. Instructions on how devices are disinfected or re-sterilized, if applicable are to be included in the instructions for use (IFU).
20. The pre-clinical and clinical data referred to in Annex X Clinical Evaluation of the MDD is required for all classes but especially so for higher risk devices.

21. All labelling and, where appropriate IFU. [Inclusion of marketing material to meet FDA requirements and to ensure appropriate controls are applied] is recommended.] This includes operator's and service manuals, where applicable.
22. A statement regarding any previous marketing history, if the device/family has been marketed elsewhere, if appropriate.
23. Catalogue numbers and descriptions.
24. If a device/family has previously been marketed, a brief statistical summary of incidents.

It is strongly recommended that manufacturers ask their selected Notified Body for guidance on the expected contents of the technical file/Design Dossier for specific devices, as early as possible in the CE marking process.

Availability of technical documentation

The technical documentation, including Design Dossiers should be readily available to present to for the Notified Body (NB) and/or Competent Authority (CA) as soon as possible upon on a request to inspect it. This obligation is the responsibility of the legal manufacturer who places the device on the EU market in their own name. Any person responsible for placing a product on the market, but not in possession of the technical documentation, such as own brand labellers or authorised representatives need to be able to state where the technical documentation is located and provide it as soon as possible via the manufacturers or third parties. Part A of the technical documentation should be made available immediately by the manufacturer and/or Authorised Representative.

The technical documentation must be kept for at least five years after the last product has been manufactured and in the case of implantable devices for fifteen years.

Language of the technical documentation

The language used for technical documentation should be maintained in the language selected by the manufacturer or as agreed to with the NB. The CA may request that the Part A information is in an official language of the CA. Part A might require translation and the requesting CA should allow time for this. Part B should normally be accepted in the language used by the manufacturer.

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Appendix 4: Guidance Notes on the Interpretation of the Essential Requirements (Medical Devices Directive 93/42/EEC, including the 2007/47/EEC Amendments)

This is in part the following is based on previous Eucomed guidance and ISO/TR 16142 Medical devices – Guidance on the selection of standards in support of recognized essential principles of medical devices. Use of harmonized standards is not mandatory but is expected and is strongly recommended.

I	GENERAL REQUIREMENTS	Guidance
1	<p>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 intended 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.</p> <p>This shall include:</p> <ul style="list-style-type: none">- reducing, as far as possible, the risk of user error due to the ergonomic features of the device and the environment in which the device is intended to be used (design for patient safety), and- consideration of the technical knowledge, experience, education and training and, where applicable, the medical and physical conditions of intended users (design for lay, professional, disabled or other users).	<p>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.</p> <p>In the case of new products, a manufacturer would typically:</p> <p>(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 EN 14971.</p> <p>(II) Review published literature and his own experience of similar devices.</p> <p>(III) Assess compliance of the product and its packaging to its own specifications and to published standards.</p> <p>(IV) Review labeling and (where appropriate) instructions for use</p> <p>(V) Review final release procedures for commercial distribution for the product.</p> <p>In the case of established products, point (iii) above will be relevant. For the rest, the manufacturer is likely to rely on a scientific review of</p>

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I	GENERAL REQUIREMENTS	Guidance
2	<p>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:</p> <ul style="list-style-type: none"> - eliminate or reduce risks as far as possible (inherently safe design 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. 	<p>the complaints history for the product in question and other similar products on the market.</p> <p>The 7th & 8th recitals (Whereas clauses) 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.</p> <p>EN 14971: 2009 Medical devices – Application of risk management to medical devices is now available and has a few small changes compared to EN 14971: 2007.</p> <p>ISO 13485: 2003 Medical devices - - Quality management systems - Requirements for regulatory purposes, in conjunction with ISO/TR 14969: 2004 Medical devices - Quality management systems - Guidance on the application of ISO 13485: 2003 are expected to be used for quality system compliance.</p> <p>Safety testing, including electrical/electronic testing where appropriate to the EN 60601 series of standards provides useful evidence of compliance to key parts of this requirement. Electronic alarms should be produced according to:</p> <p>EN 60601-1-8:2004 Medical electrical equipment -- Part 1-8: General requirements for safety - Collateral standard: General requirements, tests and guidance for alarm systems in medical electrical equipment and medical electrical systems.</p> <p>The MDD Revision has put greater emphasis on ergonomic and user related issues, similar to the human factors engineering (HFE) that FDA expects. Using FDA HFE guidance will help and use of the usability harmonised standards expected: EN 62366: 2008 Medical devices - Application of usability engineering to medical devices and/or EN 60601-1-6: 2004 Medical electrical equipment - Part 1-6: General requirements for safety - Collateral standard: Usability.</p>

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I	GENERAL REQUIREMENTS	Guidance
3	The devices must achieve the performances 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 Article 1 (2) (a), as specified by the manufacturer.	<p>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.</p> <p>Where the manufacturer is operating a quality system to Annexes II, V, or VI of the Directive, this ER will already be addressed at least in part. Use of EN 13485: 2003 and other harmonized standards is recommended. There is increased emphasis on examining the device's design in the MDD Revision irrespective of the conformity assessment route chosen.</p>
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 conditions 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.	<p>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. This needs to be updated as experience of real use is gained.</p> <p>Use of performance standards where available is recommended.</p> <p>For established products, the manufacturer will include a review of complaints history but with the MDD Revision more than this is now expected, especially for higher risk devices. Review of Annex X Clinical Evaluation is required. Use of EN 14155-1 and -2 recommended for clinical investigations, please see ER6a.</p>

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I	GENERAL REQUIREMENTS	Guidance
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. For established products, the manufacturer will review any relevant complaints history. Testing to relevant performance standards is recommended.
6	Any undesirable side-effect must constitute an acceptable risk when weighed against the performances intended.	<p>This requires identification of undesirable side effects. For new or significantly modified products the manufacturer will be expected to perform 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.</p> <p>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.</p> <p>Use of EN 14971 is very important and requires periodic updating, especially concerning significant design changes.</p>
6a	Demonstration of conformity with the essential requirements must include a clinical evaluation in accordance with Annex X.	This is a major change arising from the MDD Revision and applies to all classes of devices. Manufacturers are recommended to review the experience gained with their devices and other similar devices on the market, undertake a literature review and consider if a clinical investigation is required. If not, this needs to be scientifically justified, especially for the higher risk devices. A review of Annex X in detail as it applies to all devices is important to determine what is required and should be discussed with the Notified Body (NB) or Competent Authority (CA) as needed.

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I	GENERAL REQUIREMENTS	Guidance
		<p>Use of harmonized standards for clinical investigations are expected:</p> <ul style="list-style-type: none">• 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. <p>Refer to MEDDEV 2.7.1 Evaluation of Clinical Data, A Guide for Manufacturers and Notified Bodies (April 2003). There is an Appendix 1: Clinical evaluation of coronary stents (December 2008).</p>

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II	REQUIREMENTS REGARDING DESIGN AND CONSTRUCTION	Guidance
7	Chemical, physical and biological properties	Use harmonized standards wherever possible.
7.1	<p>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:</p> <ul style="list-style-type: none"> - 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. - where appropriate, the results of biophysical or modelling research whose validity has been demonstrated beforehand. 	<p>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.</p> <p>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 materials used for the same or very similar applications. The ISO 10993 series of standards is applicable.</p>
7.2	<p>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 exposure.</p>	<p>Any contaminants and residues in or on the device which could cause significant adverse effects should be identified. Examples include solvents; process residues; mould release agents; particulate contamination; and 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.</p>
7.3	<p>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 their 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 these products and that their performance is maintained in accordance with the</p>	<p>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</p>

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II	REQUIREMENTS REGARDING DESIGN AND CONSTRUCTION	Guidance
	intended use.	materials should be specified. The effect of ingress of liquids and gases during these procedures will need to be considered. This may call for particular instructions in the documentation supplied with the product.
7.4	<p>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 1 of Directive 2001/83/EC and which is liable to act upon the body with action ancillary to that of the device, the quality, safety, and usefulness of the substance must be verified by analogy with the methods specified in Annex I of Directive 2001/83/EC.</p> <p>For the substances referred to in the first paragraph, the notified body shall, having verified the usefulness of the substance as part of the medical device and taking account of the intended purpose of the device, seek a scientific opinion from one of the competent authorities designated by the Member States or the European Medicines Agency (EMA) acting particularly through its committee in accordance with Regulation (EC) No 726/2004 on the quality and safety of the substance including the clinical benefit/risk profile of the incorporation of the substance into the device. When issuing its opinion, the competent authority or the EMA shall take into account the manufacturing process and the data related to the usefulness of incorporation of the substance into the device as determined by the notified body.</p> <p>Where a device incorporates, as an integral part, a human blood derivative, the notified body shall, having verified the usefulness of the substance as part of the medical device and taking into account the intended purpose of the device, seek a scientific opinion from the</p>	<p>The MDD Revision has re-written and greatly expanded this ER and requires careful attention, if applicable. The concept of “usefulness” has been added for ancillary substances used with the device.</p> <p>Manufacturers need to carefully assess the use of any medicinal product used with the device and consider the primary mode of action of the combination, and discuss this with the NB and/or CA at an early stage of development before an opinion is sought by the NB from the CA.</p> <p>The medicine should be an approved product or it will require approval before it can be used.</p> <p>Manufacturers need to carefully assess the use of any blood derivative product used with the device and consider the primary mode of action of the combination, and discuss this with the NB and/or EMA at an early stage of development before an opinion is sought by the NB from the EMA. An unfavourable ruling by the EMA means the development cannot go ahead until this is resolved.</p> <p>Use of EN 14971 is vital and the clinical benefit/risk profile is important to establish.</p> <p>Ancillary substances are intended to assist in the intended use of a device and not provide a systemic treatment for the patient.</p>

Quality System Requirements For Medical Devices

II	REQUIREMENTS REGARDING DESIGN AND CONSTRUCTION	Guidance
	<p>European Medicines Agency (EMA), acting particularly through its committee on the quality and safety of the substance including the clinical benefit/risk profile of the incorporation of the human blood derivative into the device. When issuing its opinion, the EMA shall take into account the manufacturing process and the data related to the usefulness of incorporation of the substance into the device as determined by the notified body. Where changes are made to an ancillary substance incorporated in a medical device, in particular related to its manufacturing process, the notified body shall be informed of the changes and shall consult the relevant medicines competent authority (i.e. the one involved in the initial consultation), in order to confirm that the quality and safety of the ancillary substance are maintained. The competent authority shall take into account the data related to the usefulness of incorporation of the substance into the device as determined by the notified body, and to ensure that the changes have no negative impact on the established benefit/risk profile of the addition of the substance in the medical device.</p>	<p>In addition to appropriate directives, the manufacturer will normally have regard to any relevant pharmacopoeia monographs or equivalent 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.</p>
7.4	<p>When the relevant medicines competent authority (i.e. the one involved in the initial consultation) has obtained information on the ancillary substance, which could have an impact on the established benefit/risk profile of the addition of the substance on the medical device, they shall provide the notified body with advice, whether this information has impact on the established benefit/risk profile of the addition of the substance to the medical device or not. The notified body shall take the updated scientific opinion into account in reconsidering its assessment of the conformity assessment procedure.</p>	<p>It is extremely unlikely that any NB would go against the CA opinion. Gaining a favourable opinion is clearly vital and the manufacturer requires a positive view from a liability and compliance perspective.</p>
7.5	<p>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. Special attention shall be given to substances which are carcinogenic, mutagenic or toxic to reproduction, in accordance with Annex I to Council Directive 67/548/EEC of 27 June 1967 on the</p>	<p>“Leaking” includes leaching. Risks include those to patients and other persons.</p> <p>Any use of such materials will need to be considered under ER7.3 and this ER7.5 highlights the need to consider phthalates in certain</p>

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	<p>approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances.</p> <p>If parts of a device (or a device itself) intended to administer and/or remove medicines, body liquids or other substances to or from the body, or devices intended for transport and storage of such body fluids or substances, contain Phthalates which are classified as carcinogenic, mutagenic or toxic to reproduction, of category 1 or 2, in accordance with Annex I to Directive 67/548/EEC, these devices must be labelled on the device itself and/or on the packaging for each unit or, where appropriate, on the sales packaging as a device containing phthalates.</p> <p>If the intended use of such devices includes treatment of children or treatment of pregnant or nursing women, the manufacturer must provide a specific justification for the use of these substances with regard to compliance with the essential requirements, in particular of this paragraph, within the technical documentation and within the instructions for use, information on residual risks for these patient groups and, if applicable, on appropriate precautionary measures.</p>	<p>circumstances. It does not ban their use but puts the justification for use on the manufacturer. Pragmatically if safer alternatives can be used then it is clearly wise to use them. Discussion with suppliers on product specific considerations is warranted so safety data and scientific evidence can be thoroughly reviewed.</p> <p>Where applicable the product labelling and/or instructions for use must indicate the use of such substances.</p> <p>In the case of devices to treat children or pregnant women or nursing women this will require information in the instructions for use concerning residual risks and any precautionary measures to be taken.</p> <p>Manufacturers are advised to review all their materials for compliance with “REACH” the Registration, Evaluation, Authorisation and Restriction of Chemicals regulations that are in force throughout Europe.</p>
7.6	<p>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.</p>	<p>This is the counterpart of ER7.5. It should include, for example, reduction of the risk of air of fluids 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.</p>
8	<p>Infections and microbial contamination</p>	<p>Use harmonized standards wherever possible.</p>

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8.1	The devices and manufacturing process must be designed in such a way as to eliminate or reduce as far as 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 ER 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	<p>Tissues of animal origin must originate from animals that have been subjected to veterinary controls and surveillance adapted to the intended use of the tissues.</p> <p>Notified bodies shall retain information on the geographical origin of the animals.</p> <p>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 transmissible agents must be addressed by implementation of validated methods of elimination or viral inactivation in the course of the manufacturing process.</p>	<p>The full scope and interpretation of this ER may not apply to materials such as beeswax, silk or lanolin and these should be discussed with the NB and/or CA on case-by-case basis.</p> <p>It is appropriate to request certificates of origin from product 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 is given in “MEDDEV. 2.11/1 rev.2 Application of Council Directive 93/42/EEC taking into account the Commission Directive 2003/32/EC for medical devices utilising tissues or derivatives originating from animals for which a TSE risk is suspected. A guide for manufacturers and notified bodies. (January 2008).”</p> <p>Products that do not come into contact with the human body or only come into contact with intact skin such as leather orthopaedic footwear are excluded from the scope of this ER.</p> <p>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 are:</p> <ul style="list-style-type: none"> • EN ISO 22442-1: 2007 Medical devices utilizing animal tissues and their derivatives - Part 1: Application of risk management. • EN ISO 22442-2:2007 Medical devices utilizing animal tissues and their derivatives - Part 2: Controls on sourcing, collection

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		<p>and handling.</p> <ul style="list-style-type: none"> • EN ISO 22442-3:2007 Medical devices utilizing animal tissues and their derivatives - Part 3: Validation of the elimination and/or inactivation of viruses and transmissible spongiform encephalopathy (TSE) agents.
8.3	<p>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.</p>	<p>Use harmonized standards wherever possible, such as:</p> <ul style="list-style-type: none"> • EN ISO 11607-2:2006 Packaging for terminally sterilized medical devices - Part 2: Validation requirements for forming, sealing and assembly processes; and • EN ISO 11737-1:2006 Sterilization of medical devices - Microbiological methods - Part 1: Determination of a population of microorganisms on products.
8.4	<p>Devices delivered in a sterile state must have been manufactured and sterilized by an appropriate, validated method.</p>	<p>The European sterilization standards apply. This includes:</p> <ul style="list-style-type: none"> • EN 556-1: 2001 Sterilization of medical devices - Requirements for medical devices to be designated "STERILE" - Part 1: Requirements for terminally sterilized medical devices • EN 556-2: 2003 Sterilization of medical devices - Requirements for medical devices to be designated "STERILE" - Part 2: Requirements for aseptically processed medical devices.

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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. Use of relevant harmonised standards is considered vital and those to consider depending upon the method used include ISO 11135; ISO 11137 series; ISO 11140 series; ISO 11737 series; ISO 13624; ISO 14160; ISO 14180; ISO 14348; ISO 14561; ISO 14562; ISO 14563 and ISO 17665. This is not considered to be an exhaustive list of potentially useful standards.
8.6	Packaging systems for non-sterile devices must keep the product without deterioration at 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 wherever possible, especially: <ul style="list-style-type: none"> • EN ISO 11607-2:2006 Packaging for terminally sterilized medical devices - Part 2: Validation requirements for forming, sealing and assembly processes; and • EN ISO 11737-1:2006 Sterilization of medical devices - Microbiological methods - Part 1: Determination of a population of microorganisms on products.
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 ER 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 confused. Products made by competitors will have a different trademark and presentation that should avoid confusion with other products. A manufacturer may not be aware that another manufacturer has on the market or has introduced a "sterile" product similar to his own

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		“non-sterile” product. This is something to be sensitive to in post-market surveillance activities.
9	Construction and environmental properties	Use harmonized standards wherever possible.
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 performances of the devices. Any restrictions on use must be indicated on the label or in the instructions for use.	The work done to address the general essential requirements 1-6 above will normally cover this ER in particular through the reviews of the labeling and the compatibility with other products or materials indicated above. Systems need to be tested and be subject to clinical investigations where appropriate.
9.2	Devices must be designed and manufactured in such a way as to remove or minimize as far as is possible: - 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 risk 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 aging of materials used or loss of accuracy of any measuring or control mechanism.	The first and second indents are primarily for medical electrical equipment that is covered by the EN60601 series of standards. This includes specific Part 2 product standards. The third indent is primarily covered by the EN60601-1-2: 2007 collateral standard on EMC. Also refer to MEDDEV 2.2/1 Rev.1 EMC Requirements (February 1998). The fourth indent only applies where maintenance or calibration are impossible i.e. an implanted device. Use of EN 14971 should be used to consider risk assessment of parameters within the scope of this ER (and indeed all ERs).
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 or to substances which could cause combustion.	EN60601-1 covers medical electrical equipment for use in flammable atmospheres; however it does not cover oxygen enriched atmospheres. Any special requirement should be covered by the relevant EN60601 Part 2.

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10	Devices with a measuring function	Use harmonized standards wherever possible. Do refer to MEDDEV 2.1/5 Medical devices with a measuring function (June 1998).
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 manufacturer's 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 EN 60601 Part 2. This requires the intervention of a NB even for Class I devices.
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. The usability testing undertaken can assist in demonstrating compliance.
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.	The choice of units is covered by EN 60601 series for medical electrical equipment. This is a requirement for SI Units.
11	Protection against radiation	Use harmonized standards wherever possible.
11.1	General	
11.1.1	Devices shall be designed and manufactured in such a way that exposure of 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.	Note that this covers all forms of radiation e.g. light, radio frequency and heat. Medical electrical equipment is covered by the EN60601 series of standards.
11.2	Intended radiation	This requirement is covered by EN 60601-1-3: 2008 for diagnostic X-ray equipment and the relevant EN 60601 Part 2s for other equipment such as EN 60601-2-1: 1998 for electron accelerators.

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11.2.1	Where devices are designed to emit hazardous levels of radiation necessary for a specific medical 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.	Use harmonized standards, especially Part 2s, to gain presumption of compliance wherever possible. This means the manufacturer must be able to prove compliance by testing, preferably independent testing that is certified.
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.	Note that this requirement is addressed to all forms of radiation. This requirement should be covered by EN 60601-1 and also the relevant EN 60601 Part 2s.
11.3	Unintended radiation	This requirement should be covered by EN60601-1 and the relevant Part 2s.
11.3.1	Devices shall be designed and manufactured in such a way that exposure of patients, users and other persons to the emission of unintended, stray or scattered radiation is reduced as far as possible.	Use harmonized standards to gain presumption of compliance wherever possible. The manufacturer must be able to prove compliance by testing and risk analysis.
11.4	Instructions	See ER13 for general requirements and harmonised standards.
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 of avoiding misuse and of eliminating the risks inherent in installation.	For devices emitting ionizing radiation it is necessary to comply with appropriate parts of Council Directives 80/386/Euratom; 84/466/Euratom and 89/391/EEC. Use harmonized standards to gain presumption of compliance wherever possible.
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.	

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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.	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.	
12	Requirements for medical devices connected to or equipped with an energy source	Medical electrical equipment is covered by the EN60601 series of standards. Other sources of energy may have a harmonised Part 2 standard or require testing, preferably independent testing.
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 is covered by EN 60601-1-4 and Part 2 standards but EN 62304: 2006 Medical device software - Software life-cycle processes. (IEC 62304: 2006) is the harmonised standard for software that is now expected to be used.
12.1a	For devices which incorporate software or which are medical software in themselves, the software must be validated according to the state of the art taking into account the principles of development lifecycle, risk management, validation and verification.	EN 62304: 2006 Medical device software - Software life-cycle processes. (IEC 62304: 2006) is the harmonised standard for software that is now expected to be used.
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.	Primarily relevant EN 60601 series of standards and relevant Part 2s.

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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.	Primarily relevant EN60601 series of standards, including applicable Part 2s and EN 60601-1-8:2004 Medical electrical equipment -- Part 1-8: General requirements for safety - Collateral standard: General requirements, tests and guidance for alarm systems in medical electrical equipment and medical electrical systems.
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.	Primarily relevant EN 60601 series of standards and relevant 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.	EN 60601-1-2: 2007 Medical electrical equipment -- Part 1-2: General requirements for basic safety and essential performance - Collateral standard: Electromagnetic compatibility - Requirements and tests. Plus any relevant EN 60601 Part 2s.
12.6	Protection against electrical risks 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.	Primarily relevant EN 60601 series of standards and relevant Part 2s.
12.7	Protection against mechanical and thermal risks	Use harmonized standards wherever possible.
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 EN 60601-1 and any relevant EN 60601 Part 2s. Computer modelling, bench testing and field testing can all provide useful evidence of compliance.

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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. For electrical equipment see EN 60601-1 and any relevant EN 60601 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 EN 60601 Part 2s. Where alarms are fitted EN 60601-1-8: 2004 applies.
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.	Primarily relevant EN 60601 series of standards and relevant 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 surroundings must not attain potentially dangerous temperatures under normal use.	<p>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.</p> <p>The MDD Revision Article 3 now makes specific reference to the</p>

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		Machinery Directive 2006/42/EC and where a relevant hazard exists, devices which are also considered machinery must the essential health and safety requirements set out in Annex I of the Machinery Directive to the extent to which those essential health and safety requirements are more specific than the essential requirements set out in the MDD.
12.8	Protection against the risks posed to the patient by energy supplies or substances	Use harmonized standards wherever possible.
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.	This ER only applies to devices intended to supply the 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. EN 60601-1 and any relevant EN 60601 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 EN 60601-1 and specifically by the relevant EN 60601 Part 2s. The design of such devices should be inherently safe as required in ER2 for all devices.
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 EN 60601-1 and specifically by any relevant EN 60601 Part 2s. Use of symbols to EN 980 is important where possible and provided the symbols are well established and widely recognised. Usability testing is warranted for compliance.
13	Information supplied by the manufacturer	Use harmonized standards wherever possible. A translation procedure is expected by MEDDEV 2.5/5 rev.3 (February 1998).

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13.1	<p>Each device must be accompanied by the information needed to use it safely and properly, taking account of the training and knowledge of the potential users, and to identify the manufacturer.</p> <p>This information comprises the details on the label and the data in the instructions for use.</p> <p>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. 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 IIa if they can be used safely without any such instructions.</p>	<p>EN 1041: 2008 Information supplied by the manufacture with medical devices; is a vital and well established harmonized standard.</p> <p>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 products, including in vitro diagnostic (IVD) devices. Self use/test device labeling needs to be tested. The MDD Revision has raised the expectations (state of the art) for usability testing for all medical devices and this does include information supplied by the manufacturer.</p> <p>EN 60601 series standards and Parts 2 are useful to refer to and IVD standards for labeling professional use (EN 591) and self test devices (EN 592) are useful to examine. The IVD MEDDEV. 2.14/3 rev.1 Supply of Instructions For Use (IFU) and other information for <i>In-vitro</i> Diagnostic (IVD) Medical Devices (January 2007) provides insights on supplying such information by other means, i.e. electronically.</p>
13.2	<p>Where appropriate, this information should take the form of symbols. Any symbol or identification color used must conform to the harmonized standards. In areas for which no standards exist, the symbols and colors must be described in the documentation supplied with the device.</p>	<p>EN 980: 2008 Graphical symbols for use in the labeling of medical devices; is a useful well established harmonized standard.</p>
13.3 (a)	<p>The label must bear the following particulars: 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 the authorized representative where the manufacturer does not have a registered</p>	<p>Use harmonized standards to gain presumption of compliance wherever possible, including those with established symbols, i.e. EN 980.</p>

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	place of business in the Community;	
13.3 (b)	the details strictly necessary to identify the device and the contents of the packaging especially for the users;	Use harmonized standards to gain presumption of compliance wherever possible.
13.3 (c)	where appropriate, the word "STERILE";	<p>Use harmonized standards to gain presumption of compliance wherever possible, especially EN 980 for symbols. Refer for more information to:</p> <ul style="list-style-type: none"> • EN 556-1: 2001 Sterilization of medical devices - Requirements for medical devices to be designated "STERILE" - Part 1: Requirements for terminally sterilized medical devices • EN 556-2: 2003 Sterilization of medical devices - Requirements for medical devices to be designated "STERILE" - Part 2: Requirements for aseptically processed medical devices.
13.3 (d)	where appropriate, the batch code, preceded by the word "LOT", or serial number;	<p>Use harmonized standards to gain presumption of compliance wherever possible, especially</p> <p>EN 1041 for information and</p> <p>EN 980 for symbols.</p>
13.3 (e)	where appropriate, an indication of the date by which the device should be used, in safety, expressed as the year and month;	
13.3 (f)	where appropriate, an indication that the device is for single use. A manufacturer's indication of single use must be consistent across the Community;	
13.3 (g)	if the device is custom-made, the words "custom-made device";	
13.3 (h)	if the device is intended for clinical investigations, the words "exclusively for clinical investigations"	
13.3 (i)	any special storage and/or handling conditions;	
13.3 (j)	any special operating instructions;	

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13.3 (k)	any warnings and/or precautions to take;	
13.3 (l)	year of manufacturer for active devices other than those covered by e). This indication may be included in the batch or serial number;	
13.3 (m)	where applicable, method of sterilization.	EN ISO 17664:2004 Sterilization of medical devices - Information to be provided by the manufacturer for the processing of resterilizable medical devices.
13.3 (n)	in the case of a device within the meaning of Article 1(4a), an indication that the device contains a human blood derivative.	<p>EN 1041: 2008 Information supplied by the manufacture with medical devices; is a vital and well established harmonized standard.</p> <p>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 products, including in vitro diagnostic (IVD) devices. Self use/test device labeling needs to be tested with representative users. The MDD Revision has raised the expectations (state of the art) for usability testing for all medical devices and this does include information supplied by the manufacturer.</p> <p>EN 60601 series standards and Parts 2 are useful to refer to and IVD standards for labeling professional use (EN 591) and self test devices (EN 592) are useful to examine. The IVD MEDDEV. 2.14/3 rev.1 Supply of Instructions For Use (IFU) and other information for <i>In-vitro</i> Diagnostic (IVD) Medical Devices (January 2007) provides insights on supplying such information by other means, i.e. electronically.</p>
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 instructions for use.	
13.5	Wherever reasonable and practicable, the devices and detachable components must be identified, where appropriate in terms of batches, to allow all appropriate action to detect any potential risk posed by the devices and detachable components.	
13.6 (a)	Where appropriate, the instructions for use must contain the following particulars: The details referred to in Section 13.3, with the exception of (d) and (e);	
13.6 (b)	the performances referred to in Section 3 and any undesirable side-effects;	
13.6 (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;	

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13.6 (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;	Detailed manufacturers installation instructions that are validated are important to have where this is required. Part 2 standards may be of assistance for some electrical equipment.
13.6 (e)	where appropriate, information to avoid certain risk in connection with implantation of the device;	Use harmonized standards to gain presumption of compliance wherever possible. There are specific standards for some implantable devices that can provide insights on what to consider.
13.6 (f)	information regarding the risks of reciprocal interference posed by the presence of the device during specific investigations or treatment;	<p>EN 1041: 2008 Information supplied by the manufacture with medical devices; is a vital and well established harmonized standard.</p> <p>Risks clearly need to be considered in the risk assessment to EN 14971.</p> <p>Use of symbols to EN 980 wherever possible using well established and widely recognised symbols is encouraged.</p> <p>EN 60601 series standards and Parts 2 are useful to refer to and IVD standards for labeling professional use (EN 591) and self test devices (EN 592) are useful to examine. The IVD MEDDEV. 2.14/3 rev.1 Supply of Instructions For Use (IFU) and other information for <i>In-vitro</i> Diagnostic (IVD) Medical Devices (January 2007) provides insights on supplying such information by other means, i.e. electronically.</p>
13.6 (g)	the necessary instructions in the event of damage of the sterile packaging and, where appropriate, details of appropriate methods of resterilization;	
13.6 (h)	<p>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.</p> <p>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 the requirements in Section I.</p> <p>If the device bears an indication that the device is for single use, information on known characteristics and technical factors known to the manufacturer that could pose a risk if the device would be re-used. If in accordance with Section 13.1 no instructions for use are needed, the information must be made available to the user upon request;</p>	

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II	REQUIREMENTS REGARDING DESIGN AND CONSTRUCTION	Guidance
13.6 (i)	details of any further treatment or handling needed before the device can be used (for example, sterilization, final assembly, etc.);	<p>EN 1041: 2008 Information supplied by the manufacture with medical devices is a vital and well established harmonized standard.</p> <p>Risks clearly need to be considered in the risk assessment to EN 14971.</p> <p>Use of symbols to EN 980 wherever possible using well established and widely recognised symbols is encouraged.</p> <p>EN 60601 series standards and Parts 2 are useful to refer to and IVD standards for labeling professional use (EN 591) and self test devices (EN 592) are useful to examine for details. The IVD MEDDEV. 2.14/3 rev.1 Supply of Instructions For Use (IFU) and other information for <i>In-vitro</i> Diagnostic (IVD) Medical Devices (January 2007) provides insights on supplying such information by other means, i.e. electronically.</p> <p>The CE marking and its application to devices are described in Annex XII CE Marking of Conformity.</p>
13.6 (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 :	
13.6 (k)	precautions to be taken in the event of changes in the performance of the device;	
13.6 (l)	precautions to be taken as regards exposure, in reasonably foreseeable environmental conditions, to magnetic fields, external electrical influence, electrostatic discharge, pressure or variations in pressure, acceleration, thermal ignition sources, etc.;	
13.6 (m)	adequate information regarding the medicinal product or products which the device in question is designed to administer, including any limitations in the choice of substances to be delivered;	
13.6 (n)	precautions to be taken against any special, unusual risks related to the disposal of the device;	
13.6 (o)	medicinal substances, or human blood derivatives or human tissue engineered products incorporated into the device as an integral part in accordance with Sections 7.4.	
13.6 (p)	degree of accuracy claimed for devices with a measuring function.	
13.6 (q)	date of issue or the latest revision of the instruction for use.	

Appendix 5: List of Important Documents and Standards

- Council Directive 93/42/EEC of 14 June 1993, concerning medical devices (MDD) as amended by Directive 2007/47/EC.
- Council Directive 90/385/EEC of 20 June 1990, on the approximation of the laws of the Member States relating to active implantable medical devices (AIMDD).
- Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998, on *in vitro* diagnostic medical devices (IVDD).
- Commission Decision of 3 February 2009, amending Decision 2002/364/EC on common technical specifications for *in vitro*-diagnostic medical devices (2009/108/EC).
- 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).
- The Council Directive 89/686/EEC of 21 December 1989, on the approximation of the laws of the Member States relating to personal protective equipment (PPE Directive).
- Directive 2006/42/EC of the European Parliament and of the Council of 17 May 2006, on machinery (Machinery Directive).
- European Parliament and Council Directive 94/62/EC of 20 December 1994, on Packaging and Packaging Waste (PPW).
- Directive 2005/32/EC of the European Parliament and of the Council of 6 July 2005, establishing a framework for the setting of ecodesign requirements for energy-using products and amending Council Directive 92/42/EEC and Directives 96/57/EC and 2000/55/EC of the European Parliament and of the Council (EuP Directive).
- Batteries and Accumulators and Waste Batteries and Accumulators 2006/66/EC (Batteries Directive).
- Directive 2002/96/EC of the European Parliament and of the Council of 27 January 2003 on waste electrical and electronic equipment (WEEE) - Joint declaration of the European Parliament, the Council and the Commission relating to Article 9.

- Directive 2002/95/EC of the European Parliament and of the Council of 27 January 2003, on the restriction of the use of certain hazardous substances in electrical and electronic equipment, and Commission Decision of 18 August 2005, amending Directive 2002/95/EC of the European Parliament and of the Council for the purpose of establishing the maximum concentration values for certain hazardous substances in electrical and electronic equipment [2005/618/EC Maximum Concentration Values (MCV).] (RoHS Directive).
- Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006, concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC. (REACH).
- List of European Harmonized Standards (Official Journal of the European Communities).
- European Commission Europa web site for medical devices and all guidance documents.
- ISO 9001: 2008 Quality Management Systems. Requirements.
- 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.
- ISO 14971: 2009 Medical devices – Application of risk management to medical devices.
- EN 12442-1: 2007 Medical devices utilizing animal tissues and their derivatives. Application of risk management.
- EN 12442-2: 2007 Medical devices utilizing animal tissues and their derivatives. Controls on sourcing, collection and handling.
- EN 12442-3: 2007 Medical devices utilizing animal tissues and their derivatives. Validation of the elimination and/or inactivation of viruses and transmissible spongiform encephalopathy (TSE) agents.
- Canadian Medical Devices Regulations (1998) and subsequent amendments.
- Various guidance documents on the application of the Canadian Devices Regulations, please visit the Health Canada web site at: <http://www.hc-sc.gc.ca/dhp-mps/md-im/index-eng.php>
- Health Canada's policy on the use of recognized standards.
- 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.
- Global Harmonization Task Force, various documents please see www.ghtf.org.

UK MHRA Useful Guidance Documents

The main site can be accessed via www.mhra.gov.uk “How We Regulate” and then click on “Devices,” this will provide further links to all medical device information and guidance notes. Guidance at the MHRA web site is comprehensive and searching on the site will usually provide some insights on your needs, this includes (but is not limited to) the following:

- Guidance Notes for Manufacturers on Clinical Investigations to be carried out in the UK (Guidance Note 1)
- Information for Clinical Investigators (Guidance Note 3)
- Pre-clinical Assessment: Guidance for Assessors (Guidance Note 4)
- Guidance Notes for Manufacturers on Statistical Considerations for Clinical Investigations of Medical Devices (Guidance Note 17)
- Guidance on Biocompatibility Assessment (Guidance Note 5)
- Guidance Notes for Manufacturers of Class 1 Medical Devices (Guidance Note 7)
- Guidance Notes for the Registration of Persons Responsible for Placing Devices on the Market (Guidance Note 8)
- Guidance Notes for the Registration of Person Responsible for Placing *In-Vitro* Diagnostic Medical Devices on the Market (Guidance Note 18)
- Guidance Notes on In Vitro Diagnostic Medical Devices Directive 98/79/EC (Guidance Note 19)

Directives Bulletins

- The CE Marking (Bulletin 2)
- The Vigilance System (Bulletin 3)
- Conformity Assessment Procedures (Bulletin 4)
- The Notified Body (Bulletin 6)
- Information about the EC Medical Devices Directives (Bulletin 8)
- The Classification Rules (Bulletin 10) but do refer to MDD Revision too.
- Sale and Supply of In Vitro Diagnostic Medical Devices (IVDs) (Bulletin 1)
- Standards (Bulletin 3)
- Medical Devices and Medicinal Products (Bulletin 17)

- The Medical Devices Regulations: Implications on Healthcare and other Related Establishments (Bulletin 18)
- Own Brand Labeling and Rented Products (Bulletin 19)
- Conformity Assessment Procedures under the In Vitro Diagnostic Medical Devices Directive 98/79/EC (Bulletin 20)
- Application for the Exceptional use of Non-Complying Devices (Bulletin 21, Humanitarian Bulletin)

Other Useful MHRA 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
- Joint Replacement Implants - Guidance on the Vigilance System (VG01)
- Artificial Heart Valves - Guidance on the Vigilance System (VG02)
- Artificial Breast Implants - Guidance on the Vigilance System (VG03)
- Artificial Coronary Stents - Guidance on the Vigilance System (VG04)
- IVD Blood Glucose Meters in POCT or Home Use - Guidance on the Vigilance System (VG05)
- Inferior Vena Cava - Guidance on the Vigilance System (VG06)
- Intraocular Lenses - Guidance on the Vigilance System (VG07)
- Optical Flyer – The Application of the EC Medical Devices Directive to Ophthalmic Medical Practitioners, Optometrists, Dispensing Opticians and Manufacturing Opticians
- Guidance Notes for Manufacturers of Custom-made Devices (Guidance Note 9)
- Guidance Notes for Manufacturers of Dental Appliances (Custom Made Devices) (Guidance Note 10)
- Guidance Notes for Manufacturers of Prosthetic and Orthotic Appliances (Guidance Note 16)

There are further links and more information; you should be able to find useful insights on your products and, if not you can contact the MHRA by email to find further information.

Appendix 6: Comparison Table of ISO 13485: 2003 and FDA's Quality System Regulation

The table below lists the corresponding clauses of ISO 13485:2003 and the FDA Quality System Regulation that is useful as a reference. This table is important when identifying gaps in implementation or demonstrating to regulatory authorities how compliance is achieved with ISO 13485 and FDA QS regulation, often call current Good Manufacturing Practice (cGMP).

ISO 13485:2003	FDA Quality System Regulation
1. Scope	820.1 Scope 820.1 (a) Applicability
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 and (b) Training
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
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

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ISO 13485:2003	FDA Quality System Regulation
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
7.2.1 Determination of Requirements Related to Product 7.3.2 Design & Development Inputs	820.30 (c) Design Input
7.3.3 Design & Development Outputs	820.30 (d) Design Output
7.3.4 Design & Development Review	820.30 (e) Design Review
7.3.5 Design & Development Verification	820.30 (f) Design Verification
7.3.6 Design & Development Validation	820.30 (g) Design Validation 820.70 (i) Automated Processes
7.3.7 Control of Design & Development Changes	820.30 (i) Design Changes 820.70 (b) Production & Process 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
7.4.1 Purchasing Process	820.50 Purchasing Controls 820.50 (a) Evaluation of Suppliers, Contractors & Consultants
7.4.2 Purchasing Information	820.50 (b) Purchasing Data
7.4.3 Verification of Purchased Product	820.80 (a) General
7.5.4 Customer Property	820.80 (a) General
7.5.3 Identification & Traceability	820.60 Identification 820.65 Traceability

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ISO 13485:2003	FDA Quality System Regulation
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 (c) 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 Validation 820.170 (b) Installation
7.1 Planning of Product Realization 8.1 Measurement , Analysis & Improvement	820.80 (a) Receiving, In-process & Finished Device Acceptance – General
7.4.3 Verification of Purchased Product	820.80 (b) Receiving Acceptance Activities
8.2.4 Monitoring & Measurement of Product	820.80 (c) In-process Acceptance Activities
8.2.4 Monitoring & Measurement of Product	820.80 (d) Final Acceptance Activities
7.5.3 Identification & Traceability	820.80 (e) Acceptance Records
7.6 Control of Monitoring & Measuring Devices	820.70 (c) Environmental Control 820.72 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
7.5.3 Identification & Traceability	820.86 Acceptance Status
8.3 Control of Non-conforming Product	820.90 Nonconforming Product 820.90 (a) Control of Nonconforming Product
8.3 Control of Non-conforming Product	820.90 (b) Nonconforming Review & Disposition
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

Quality System Requirements For Medical Devices

ISO 13485:2003	FDA Quality System Regulation
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 Related Activities 820.198 Complaint Files
6.4 Work Environment 7.5.1 Control of Production & Service Provision	820.120 Device Labeling 820.130 Device Packaging 820.140 Handling
7.5.5 Preservation of Product	820.150 Storage
7.5.5 Preservation of Product	820.130 Device Packaging
7.5.5 Preservation of Product	820.130 Device Packaging
7.5.5 Preservation of Product	820.160 (a) Distribution Control for Finished Products
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
8.2.2 Internal Audit 8.2.3 Monitoring & Measurement of Processes	820.22 Quality Audit
6.2.2 Competence, Awareness & Training	820.25 (b) Training
7.5.1 Control of Production & Service Provision	820.200 Servicing
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 United States Food and Drug Administration (FDA) can charge a fee for the review of medical devices. There is a provision within MDUFMA that allows for a reduction in fees for small businesses.

To pay a reduced fee, a firm must qualify as a small business with gross receipts or sales of no more than US\$100 million, including the gross receipts or sales of all the firm's affiliates. To obtain a one-time waiver of the fee for a first (ever) premarket application (premarket approval application, biologics license application, product development protocol, or premarket report), a firm must qualify as a small business with gross receipts or sales of no more than US\$30 million, including the gross receipts or sales of all the firm's affiliates. Both businesses headquartered in the United States and foreign businesses headquartered outside the United States are eligible to apply to qualify as a small business.

The U.S. FDA has issued a guidance document on Medical Device User Fee Small Business Qualification and Certification, which includes the necessary application forms. The guidance document is available on the FDA's website at:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/MedicalDeviceUserFeeandModernizationActMDUFMA/default.htm>

Section III of the form for Foreign Small Business Qualification Certification must be completed by the applicant firm's National Taxing Authority. For firms headquartered in Canada, the National Taxing Authority is the Canada Revenue Agency (CRA):

<http://www.cra-arc.gc.ca/>

Firms should call the CRA's business enquiries number for direction to the appropriate regional contact who can provide the necessary certification:

Canada Revenue Agency

Telephone Enquiries

Businesses and self-employed individuals: 1-800-959-5525

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.

Canadian Medical Devices Conformity Assessment System (CMDCAS)

The quality system conformity assessment system requirement to which ISO 13485 needs to be audited to be acceptable to Health Canada for medical device registration purposes.

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. For example, under the MRA between Canada and the EU, Canadian registrars can assess a Canadian manufacturer's compliance against EU requirements and EU notified bodies can assess an EU manufacturer's compliance against Canadian requirements.

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 which is applied to a product demonstrating it conforms to the requirements of appropriate European directives. 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 appropriate directives.

CFR

US Code of Federal Regulations.

Controlled Documents

These are 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 are also controlled documents. These

include: relevant ISO, EN, ANSI and other standards, relevant medical devices regulations, and client-supplied product specifications, drawings, and instructions.

Declaration of Conformity

This is a formal statement, by a manufacturer, that a product complies with the relevant essential requirements, of the appropriate European directives.

Design Dossier

This is a comprehensive 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)

This is FDA term for a compilation of records that describe the design history of a finished device.

Device Master Record (DMR)

This is FDA term for a compilation of records containing the procedures and specifications for a finished device.

Device History Record (DHR)

This is 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.

European Medicines Agency (EMA)

EMA was known as the European Agency for the Evaluation of Medicinal Products until 31 December 2009 but is now known as the European Medicines Agency (EMA) but the logo and short version “EMA” remains on the web site. “EMA” may also be used by others as an abbreviation. Please see:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000235.jsp

EMA is the pan-European regulator that aims to harmonize European regulations for medicinal products and to which a single EU marketing authorisation for medicines can be made

Essential Requirements

A list of requirements contained within the MDD (Annex I) which, 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 which regulates the manufacture of food, drugs, biologics and devices in the US.

Federal Food, Drug and Cosmetic Act (FD&C Act)

This is one of the major laws which give 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. It is sometimes referred to as Current Good Manufacturing Practice (cGMP).

Harmonized Standard

In Europe -- A technical specification (European Standard or harmonized document) adopted by the European Commission through CEN (European Committee for Standardization) or CENELEC (European Committee for Electrotechnical 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 web site.

Health Canada

This is 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 concerns 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 9001: 2008 Quality management systems. Requirements

The International Organization for Standardization models for quality assurance. ISO 9001:2008 is the model for design, development, production, and installation and servicing. It is not specific to medical devices, whereas ISO 13485: 2003 that is based on is.

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; it does not require continual improvement or customer satisfaction.

IVD

In Vitro Diagnostic.

IVDD

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, software, 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;

And 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 all the medical directives.

Notified Body

A commercial entity (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; it contains 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 European medical directives 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 performance, quality system approval, product approvals and all associated documents.

Vigilance Reporting

A requirement included under the European medical directives, whereby Member States must ensure that adverse incidents involving medical devices in the marketplace are reported to the relevant Competent Authorities and recorded. Manufacturers must put in place procedures to respond to such reports, by evaluating the causes, reporting findings to Competent Authorities and take the necessary corrective actions.