

The Manufacturer's Guide to the Revised MDD



Introduction

The long-anticipated revisions to the Medical Device Directive (MDD 93/42/EEC) and the Directive for Active Implantable Devices (90/385/EEC) were published in the Official Journal of the European Union on September 21, 2007. The amendments, along with changes to Directive 98/8/EC (concerning the placing of biocidal products on the market) are combined in to the change Directive 2007/47/EC.

The EU member states should have implemented 2007/47/EC nationally by December 21, 2008 (15 months after publication), and the changes will become mandatory on March 21, 2010 (30 months after publication). 2007/47/EC can be difficult to comprehend, since it is a lengthy document only listing the changes, but it may help with interpretations as it provides justifications for the changes made.

The European Commission has released a consolidated version of the MDD 93/42/EEC incorporating all changes from the change Directive. The consolidated version, as well as 2007/47/EC, can be downloaded from the Commission's webpage: http://ec.europa.eu/enterprise/medical_devices/legislation_en.htm

This article aims to ease your own understanding of the MDD, so you can proactively address the changes it now contains. Any underlining in the quoted text has been added by Intertek to highlight essential wording.

Please note that this article only covers the MDD and the changes that directly impact medical device manufacturers. This is not an exhaustive list, and does not include the full wording of all changes. Refer to 2007/47/EC or the consolidated version of 93/47/EEC for complete details.

Throughout the text, the abbreviation "NB" is used for Notified Body, and "MDD" for the Medical Device Directive 93/42/EEC including amending directives.

Who will be affected by the changes?

All device manufacturers will be at least partly affected by these changes. For example, the increased requirements for clinical investigations will affect all manufacturers. Also, changes to the Essential Requirements mean that all manufacturers will need to address the changes and update their Technical Files. Other changes will only affect manufacturers of devices that will be reclassified, or specific devices that contain phthalates. Changes affecting manufacturers usually also affect the Notified Bodies' assessments.

Apart from the changes directly affecting the manufacturer, the revision contains some clauses aimed at the authorities, such as transparency and cooperation between the member states. Some clauses increase the European Commission's authority and give it the right to make changes to the Directives through a shorter process than was previously used (but only in certain cases, such as changes to classification criteria, distribution of information to the user, confidentiality, and changes involving clinical investigations). This means that there could be further changes to the Directive in the future, if the Commission finds it necessary to do so for these specific issues.

Major changes to the MDD

Reprocessing of sterile, single use devices

The revised Directive now includes a definition of "single use":

(n)... a device intended to be used once only for a single patient.

It also states that the marking for single use must be consistent within the EEA. A manufacturer cannot mark a device "for single use" in one country and not so in other countries. The Directive also adds requirements for the manual, which should include:

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 were to 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.

Revisions to the main text of the MDD

Article 1: Scope and definitions

The definition of “medical device” has been slightly changed, to clearly state the current interpretation that software can be a medical device. The wording is now (new wording in blue):

*‘medical device’ means any instrument, apparatus, appliance, **software**, material or other article, whether used alone or in combination, including the software **intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes** and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of:...*

Article 1 still clearly states that transplants of tissues or cells of human origin, or products incorporating such substances, are not covered by the MDD (with one exception regarding derivative of human blood/plasma, 4a).

New definitions are also included for “clinical data,” “device subcategory” and “generic device group;” these are discussed in the chapter for Annex X, Clinical evaluation and for Annex II respectively.

Machinery Directive

There is a new reference to the Machinery Directive, MD 2006/42/EC, which has also been revised and becomes compulsory on 29 December 2009. In the old version, medical devices were excluded, but this wording has now been removed. Therefore, wording to address requirements of the Machinery Directive has been added to the MDD to avoid the need of conformity assessment through both Directives.

If a device is considered a machine as defined in the Machinery Directive, and a relevant hazard exists, the manufacturer needs to evaluate which of the essential

health and safety requirements are applicable to the device and if they are more specific than those in the MDD, and if so, address these. Documentation to show compliance should be part of the technical documentation. However, the conformity assessment is only through the MDD.

Article 12: Particular procedures for systems and procedure packs

The heading of this article has changed to *Particular procedure for systems and procedure packs and procedure for sterilization*. For the sterilization of the devices covered by this article, the manufacturer can now only choose between Annex II and V for conformity (where before they could choose from Annex IV, V or VI).

Article 14: Registration / information

The Directive now includes a requirement for the manufacturer to designate a single authorised representative for devices in all classes when the manufacturer does not have a registered place of business in the Community. The interpretation of “a single authorised representative” is that it is possible for a manufacturer to have several authorised representatives but not for the same products. At least for all devices of the same model, there shall be a single authorised representative. For devices that need to be registered with a Competent Authority (Class I devices, custom-made devices, and devices in accordance with Article 12), the authorised representative shall register these in the member state in which it has its registered place of business.

The member states are allowed to request any necessary information to identify products in Class IIa, together with their label and user manual, when these are put into service within their territory. This opportunity was previously only available for Class IIb and III devices. (Some countries have introduced requirements for registration of all devices in their territory.)

Article 15: Clinical investigations

This article includes increased requirements on the exchange of information, and the review by involved authorities and ethics committees. As before, the manufacturer must follow the procedure referred to in Annex VIII and notify the competent authorities when he wishes to perform a clinical investigation. A new requirement is that the authorities shall also be informed when the investigation is terminated:

The manufacturer or his authorised representative shall notify the competent authorities of the Member States concerned of the end of the clinical investigation, with a justification in case of early termination. In the case of early termination of the clinical investigation on safety grounds this notification shall be communicated to all Member States and the Commission.

Article 18: Wrongly affixed CE marking

This article has been extended to include cases where CE marking is missing in violation of the Directive.

Revisions to Annex I Essential requirements

Annex I now includes a clear statement of the importance of adapting devices to both the user and the environment in which the devices will be used. The following statements were added to the general requirements:

- reducing, as far as possible, the risk of use 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).*

Therefore it follows that it is important to identify the user and the environment in which the device will be used. This requirement should already have been addressed through, for example, risk analysis and validation activities. However, the activities related to this area may need to be summarised and referenced to clearly show that the requirement has been addressed. Useful information may be collected through evaluation of customer feedback, complaints, and vigilance cases. But it is important that if the result of feedback such as a complaint identifies a use error, the analysis does not stop at that conclusion, but goes deeper to identify a root cause (to see if, for example, the design, manual, training, etc. may not be appropriate).

Harmonised standards that cover usability are:

- EN 60601-1-6:2007 Medical electrical equipment — Part 1-6: General requirements for basic safety and essential performance — Collateral standard: Usability (IEC 60601-1-6:2006). This replaces EN 60601-1-6:2004.
- EN 62366:2008 Medical devices — Application of usability engineering to medical devices (IEC 62366:2007).

6a: Clinical evaluation (new section)

Demonstration of conformity with the essential requirements must include a clinical evaluation in accordance with Annex X.

This replaces essential requirement number 14, which has been removed. See the chapter on Annex X for details.

7.4: Devices incorporating medicinal substances or substances derived from human blood

A substantial amount of text has been added to make the assessment process of this type of device clearer, and to better explain the roles of the involved parties. Similar text has also been added in Annexes II and III. For example, the authorities (EMA or national authorities) must give their judgment within 210 days.

7.5: Leaking substances

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.

The wording above was the complete requirement of 7.5 in the old version, and it still remains. As a precautionary measure, and to allow the identification of certain devices that contain phthalates, the following text has been added to Section 7.5 of Annex I:

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 approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances.

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.

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.

A standard for the phthalate marking (prEN 15986) is being fast tracked but is not expected to be ready before 21 March 2010. The marks in the draft version could be used in the meantime but will need to be explained in the manual; there is a high probability that these will be accepted, but this can not be guaranteed. The following are examples of the proposed marking for different types of phthalates; the identifier/s should be placed adjacent to the symbol:



Note that since the change Directive 2007/47/EC was approved, a new EU regulation has been adopted that will replace the referenced directive 67/548/EEC. This is EU Regulation 1272/2008 on classification, labelling and packaging of substances and mixtures, often called CLP. 1272/2008, the Annex that corresponds to Annex I in the Directive, is Annex VI in this EU regulation.

12.1a: Software

Software must now be:

...validated according to the state of the art taking into account the principles of development lifecycle, risk management, validation and verification.

Since this is an essential requirement, the manufacturer must validate the software (integrated or stand-alone), regardless of the class of the device or the conformity annex chosen. The standard EN 62304:2006, *Medical device software — Software life-cycle processes* (IEC 62304:2006) has been harmonised and is a useful tool. The EN (IEC) 60601 series also contain requirements on software/programmable circuits, but this scope is more limited.

13: Information to the user

Along with the changes regarding single use devices (described on page 3 of this document), and the requirements concerning phthalates, there is one minor addition for the manual regarding revision control:

(q) date of issue or the latest revision of the instructions for use.

Revisions to Annex II

The rules for archiving still state five years for most devices, but in the case of implantable devices, this has been increased to *at least 15 years after the last product has been manufactured.*

Section 7: Use of Annex II for devices in Class IIa and Class IIb

The following text regarding review of technical documentation by the Notified Body has been added:

7.2. For devices in Class IIa the notified body 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.

7.3. For devices in Class IIb the notified body 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.

7.4. In choosing representative sample(s) the notified body shall 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 in accordance with this Directive. The notified body shall document and keep available to the competent authority its rationale for the sample(s) taken.

7.5. Further samples shall be assessed by the notified body as part of the surveillance assessment referred to in Section 5.

The definitions of “device subcategory” and “generic device group” have been added to the definitions listed in Article 1 at the start of the directive:

(l) "device subcategory" means a set of devices having common areas of intended use or common technology;"

(m) "generic device group" means a set of devices having the same or similar intended uses or commonality of technology allowing them to be classified in a generic manner not reflecting specific characteristics.

Most countries' authorities already require that the Notified Body review the technical documentation as part of their assessment, but until now this has not been specifically stated. The review depth and the sampled numbers have varied. The addition clarifies that technical documentation must be part of a Notified Body's assessment, and provides guidelines on how it will be sampled – therefore giving all Notified Bodies the same rules to work by.

NBOG (Notified Body Operations Group, with members from the Competent Authorities) has issued document BPG 2009-4 “Guidance on Notified Body's Tasks of Technical Documentation Assessment on a Representative Basis.” According to this guidance, the “generic device group” used for Class IIb is the same as that used

by the GMDN system; therefore for the IIb, the GMDN terms can be used as a basis for sampling. For class IIa it is suggested that the grouped collective terms uses another guidance from NBOG, the BPG 2009-3, to define scope expressions for the notification of NB.

In practice, for initial audits, the NB is expected to identify the complete range of Class IIa and IIb products manufactured and define a suitable sampling plan. This should be done based on the numbers of generic device groups and grouped collective terms. The sampling shall continue during each certification period. The reviews may or may not be done in conjunction with the surveillance audits, and can be performed on-site and/or off-site according to the procedures of the NB. As long as there is still documentation that has not been reviewed, at least one sample shall be reviewed each year.

The BPG documents from NBOG can be downloaded at the website www.nbog.eu.

Revisions to Annexes III - VII

Annexes III – VII now contain the same rules for archiving that appear in Annex II.

Text has been added to Annex III on the conformity procedure for devices that incorporate medicinal products or derivatives from human blood, in line with the clarifications added to Annex II for these types of products.

Annexes V and VI also have the same added requirement for assessment of technical documentation for devices in Class IIa.

In all Annexes referencing the quality system, there is also an addition (in point 3.2 b) that emphasizes the importance of control of subcontractors:

– where the manufacture and/or final inspection and testing of the products, or elements thereof, are carried out by a third party, the methods of monitoring the efficient operation of the quality system and in particular the type and extent of control applied to the third party.

This text was added to address several particular issues concerning an adequate working of the quality system. The reasoning for this is stated as:

In the light of the increased use of third Parties to carry out the design and manufacture of devices on behalf of the manufacturer, it is important that the manufacturer demonstrates that he applies adequate controls to the third party to continue to ensure the efficient operating of the quality system.

In Annex VII, EC Declaration of Conformity, section 3, the list of items to be contained in the technical documentation has been clarified and extended to contain the intended use of the device, in addition to the description of the device and any planned variants. For devices that will be delivered sterile, the documentation must contain a description of the method of sterilization, as well as the validation report. The documentation must also contain the solutions adopted to show conformance with the general essential requirements (Annex I, part 1.2), the pre-clinical validation, and the clinical evaluation in accordance with Annex X.

Manufacturers of Class I sterile devices, or devices with a measuring function, can now choose Annex II in addition to Annexes IV, V or VI (but in reality, NBs usually do not accept to use Annex IV or VI for sterile devices, as these are unsuitable for verification of the process of obtaining sterility). As before, the application of the Annexes is limited for this type of products, so in reality there is little difference.

Revisions to Annex VIII

Devices for clinical investigations

The statement required in Annex VIII must, in addition to the old requirements, also contain the following points. This statement is supplied to the Competent Authority when notifying them of a clinical investigation.

- *the investigator's brochure,*
- *the confirmation of insurance of subjects,*
- *the documents used to obtain informed consent,*
- *a statement indicating whether or not the device incorporates, as an integral part,*

*a substance or human blood derivative referred to in Section 7.4 of Annex I,
– a statement indicating whether or not the device is manufactured utilising tissues of animal origin as referred to in Directive 2003/32/EC*

The following text has been added to the section listing the documentation that the manufacturer needs to keep available for the Competent Authorities:

*– if the device incorporates, as an integral part, a substance or human blood derivative referred to in Section 7.4 of Annex I, the data on the tests conducted in this connection which are required to assess the safety, quality and usefulness of that substance or human blood derivative, taking account of the intended purpose of the device,
– if the device is manufactured utilising tissues of animal origin as referred to in Directive 2003/32/EC, the risk management measures in this connection which have been applied to reduce the risk of infection,*

Custom-made devices

For manufacturers that produce custom-made devices, a new requirement is that the manufacturer must review and document any experience gained in the post-production phase, including the provisions referred to in Annex X, and implement appropriate means to apply any necessary corrective action. A requirement for a vigilance system has also been added.

There are also additional requirements on the documentation that the manufacturer needs to keep available for the Competent Authority:

3.1. For custom-made devices, documentation, indicating manufacturing site(s) and allowing an understanding of the design, manufacture and performances of the product, including the expected performances, so as to allow assessment of conformity with the requirements of this Directive.

Also, in this case, the manufacturer needs to produce a statement which shall follow the product and shall be made available for the patient for which the product is intended.

Revisions to Annex IX Classification rules

Definitions

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

This has been added as a clarification, since for years it has been regarded as such by involved parties. As with any other device, it must first be decided that the software falls under the definition of a “medical device,” or as an accessory to a medical device, before the appropriate classification can be decided.

The definition of the central circulatory system has been extended to include the *arcus aorta* and the *aorta descendens to the bifurcatio aortae*.

Implementing rules

The revision clarifies how duration shall be calculated. This may result in a higher class, as some invasive devices that were previously regarded as used for less than 60 minutes may now exceed this limit:

...continuous use means “an uninterrupted actual use of the device for the intended purpose”. However where usage of a device is discontinued in order for the device to be replaced immediately by the same or an identical device this shall be considered an extension of the continuous use of the device.

Rule 5

This rule has been slightly changed to remove the incoherence in the classification rules that caused invasive devices in body orifices and intended for connection to an active Class I medical device to not be classified at all.

If your device is invasive in a body orifice and intended for connection to an active device in Class I, the class of your device will be dependent on which of the indents in the rule is applicable (mostly dependent on the time of continuous use).

Rule 6

This rule now specifies that all surgically invasive devices intended for transient use are in Class IIa unless they are:

- intended specifically to control, diagnose, monitor or correct a defect of the heart or of the central circulatory system through direct contact with these parts of the body, in which case they are in Class III

Rule 15

This rule specifies that all devices intended specifically to be used to disinfecting medical devices are in Class IIa, and adds the following exception:

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

Rule 16

The limitation to non-active devices has been removed, which means that digital systems are now included. The new wording is:

Devices specifically intended for recording of X-ray diagnostic images are in Class IIa.

Effects of classification changes

If a product changes classification, obviously the technical documentation needs to be revised to this effect. But it may also necessitate a change in the conformity assessment route. A product that becomes Class IIb requires the use of Annex II; if the manufacturer has an Annex V certificate today, an upgrade audit to Annex II is required.

Class III devices also require that the manufacturer uses Annex II. Class III also requires that a Design Dossier review is performed. These activities need to be completed before 21 March 2010 to avoid interruption to the certification.

As stated before, reclassification to Class IIa or IIb can also impact the sampling of Technical Files for review.

Revisions to Annex X, Clinical evaluation

Annex X has been extensively reworded and clarified, to mirror the importance of clinical data and the evaluation of this data. References to clinical data have also been added to other relevant articles and Annexes of the Directive. This serves to strengthen the documentation requirements.

Below are some notable excerpts from Annex X:

1.1c 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.

1.1d Where demonstration of conformity with essential requirements based on clinical data is not deemed appropriate, adequate justification for any such exclusion has to be given based on risk management output and under consideration of the specifics of the device/body interaction, the clinical performances intended and the claims of the manufacturer. Adequacy of demonstration of conformity with the essential requirements by performance evaluation, bench testing and pre-clinical evaluation alone has to be duly substantiated.

2.3.5. All serious adverse events must be fully recorded and immediately notified to all competent authorities of the Member States in which the clinical investigation is being performed.

A manufacturer needs to review the existing data to see if it needs to be updated to be in conformance with the new requirements. The quality and presentation of the data may need to be addressed. For a product that has been on the market for some time, there should be available data that can be assessed and evaluated.

There are a number of MEDDEV guidance documents that relate to clinical data, clinical investigations, and clinical evaluations:

- MEDDEV 2.7.1 (2003) Evaluation of Clinical Data. A guide for manufacturers and notified bodies

- MEDDEV 2.7.1 Annex 1 (2008) Clinical Evaluation of Coronary Stents
- MEDDEV 2.12-1 (2004) Guidelines on Post Market Clinical Follow-up (PMCF) – this also discuss PMS plans or strategies; and the concept of an “equivalent device”.
- MEDDEV 2.7.2 (2008) Guide for competent authorities in making an assessment of clinical investigation notification.

Note that the older MEDDEVs will reference the wording of the old version of the MDD. However, the concept and process of how to perform a clinical evaluation is generally in line with the new requirements.

The harmonised standard for clinical investigations is EN ISO 14155 part 1 and 2. Part 1 includes an advisory annex for the “Literature route”.

Conclusion

The changes outlined in this document represent some of the first major revisions to the MDD in almost 15 years, outside of occasional changes on specific issues. They may seem overwhelming at first glance – and undoubtedly they will be for some manufacturers, such as those facing reclassification. But many of the changes are clarifications of what has been intended all along, or confirmations on interpretations that are already widely used. A manufacturer, especially of high risk devices, should already have most of what is required with the exception of the specific, totally new requirements. Perhaps it is with regard to the low risk devices that a manufacturer may really feel that the bar has been raised. The clarification on Technical File reviews will, depending on the present regime applied by a manufacturer’s NB, result in increased sampling for most and possibly also a more in-depth review.

All manufacturers need to review the revised MDD in detail as soon as possible to identify the specific requirements that will affect them. This will allow them to establish action plans with reasonable timeframes if any “gaps” are identified. As always, the Technical File is a living document and need to be updated as a result of

product changes, standard revisions, and changes to regulatory requirements. Also, the revised MDD specifically identifies data that needs to be kept updated within the Technical File.

As usual, it will be difficult to estimate the full effect of the changes until the revision has been in use for some time and praxis has evolved.

Some interpretations and guidance documents have been developed by the authorities in the last two years, and there will probably be more, including updates to the MEDDEVs. But the manufacturer cannot wait any longer as the deadline draws near. Advance planning will be the key for manufacturers to effectively implement the new requirements and adjust to the changes before they become mandatory. This is especially essential for products that are affected by the larger changes, so that the manufacturer can minimize the risk of an interruption to the EC certification.