

New European Device Clinical Requirements: Part 1

By 21 March 2010, companies marketing medical devices in Europe will need to demonstrate compliance with new and clarified European requirements on clinical data and other clinical requirements. Part 1 of this two-part article discusses the requirements on clinical data and evaluation. Part 2 will address the requirements on clinical investigations, postmarket clinical follow up and conformity assessment of clinical data.

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Revising Directive

The revising Directive (2007/47/EC), published on 21 September 2007¹ amends the Medical Device Directive (MDD) (93/42/EEC) and the Active Implantable Medical Device Directive (AIMDD) (90/385/EEC). It does not amend the In Vitro Diagnostic Directive (98/79/EC). Some of the most important clarifications and new requirements that it introduces relate to clinical data, clinical evaluation, clinical investigations, postmarket clinical follow-up and conformity assessment of clinical data. Where this article discusses the amendments made to the MDD, it should be understood that analogous amendments have also been made to the AIMDD.

The amendments of the revising Directive become mandatory on 21 March 2010. This means that any product placed on the market or put into service on or after that date must comply with the revised MDD and AIMDD. For this reason, manufacturers should already have programmes in place to ensure that they comply with the revised Directives, or will have by the time the amendments become mandatory. If this is not done, those companies that market medical devices that require Notified Body involvement risk problems arising during Notified Body assessments and certification audits. If serious enough, these could affect a company's quality system certification status. This article discusses the new or clarified clinical requirements and how companies can meet them.

New clinical data definition

The revising Directive introduces a definition for clinical data in the MDD and AIMDD. In the MDD, the new definition is in Article 1(k), which states that "clinical data means the safety and/or



performance information that is generated from the use of a device.

Clinical data are sourced from

- clinical investigation(s) of the device concerned; or
- clinical investigation(s) or other studies reported in the scientific literature, of a similar device for which equivalence to the device in question can be demonstrated; or
- published and/or unpublished reports on other clinical experience of either the device in question or a similar device for which equivalence to the device in question can be demonstrated."

This new definition should help to reduce the uncertainty that some companies have faced in trying to understand exactly what "clinical data" means. In addition, the inclusion of unpublished reports as a source of clinical data promotes harmonisation with United States (US) requirements. In the US, the inclusion of unpublished adverse information and a summary of all other unpublished information (whether adverse or supportive) are required in an Investigational Device Exemption application. This is specified in Section 21 Code of Federal Regulations (CFR) 812.27, Report of Prior



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Investigations; and the inclusion of unpublished data is also required under the US Premarket Approval regulations in 21 CFR 814.

Current clinical data requirements

The importance of clinical data in determining whether or not medical devices meet the safety and performance requirements of the European medical device Directives is not new. The MDD, which has been mandatory for more than 10 years, requires that, as a general rule, clinical data are needed to confirm conformity with the Essential Requirements related to patient and user safety, an acceptable benefit–risk ratio, and the achievement of device performance as intended by the manufacturer.

The current requirement for clinical data is specified in Section 1.1 of Annex X of the MDD, which also states that clinical data are needed to confirm safety and performance requirements in particular for implantable devices and devices in Class III. Some medical device companies have incorrectly interpreted this to mean that clinical data are not needed when medical devices are not implantable or not in Class III. As a result, the technical documentation for medical devices in lower risk categories often lack adequate clinical data on which to base conformity with safety and performance requirements.

New emphasis on clinical data

Directive 2007/47 revises the Clinical Evaluation Annexes of the MDD and AIMDD in an important way with regard to the need for clinical data. In the MDD, revised Section 1.1 of Annex X, Clinical Evaluation, states:

“as a general rule, confirmation of conformity with the requirements concerning the characteristics and performances referred to in Sections 1 and 3 of Annex I, under the normal conditions of use of the device, and the evaluation of the side-effects and of the acceptability of the benefit-risk ratio referred to in Section 6 of Annex I, must be based on clinical data.”

Annex I lists the Essential Requirements, which form the cornerstone of the medical device Directives. To be placed on the market or put into service, all medical devices must meet the Essential Requirements that apply to them. Sections 1 and 3 of Annex I of the MDD are Essential Requirements that concern the need to design and manufacture devices to ensure that they are safe and perform as intended. Section 6 is the Essential Requirement that concerns the need for any undesirable side effect to constitute an acceptable risk when weighed against the performances intended, in other words, there must be an acceptable benefit–risk ratio.

The revised text of Section 1.1 of Annex X of the MDD (and analogous text in the AIMDD) no longer include references to implantable devices and devices in Class III. Thus, it clarifies that appropriate clinical data are required for all classes of devices, not just those in higher risk categories. In addition, characteristics and performances in Section 1 of Annex I that need to be confirmed with clinical data have been expanded. Directive 2007/47/EC has amended Section 1 of Annex I and includes: →

- ■ 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)
- 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).

These are important changes because some companies may not have sufficient clinical data to meet the requirements of the revised MDD and AIMDD. The determination of compliance with these new and clarified clinical data requirements will now need to be done. In addition, where ergonomic features are important to the safety and performance of the device, usability testing may be needed. Depending on the design of the usability tests, they may be considered to be clinical studies if the devices are actually being used by patients. In this case, the studies will need to meet local and European requirements for conducting clinical investigations. In spite of the increased clarity on the need for clinical data in the revised MDD and AIMDD, it is important to mention that they include requirements that must be met if the manufacturer believes that clinical data are unnecessary for demonstrating conformity with the Essential Requirements. This is discussed later.

New Essential Requirement

The need to conduct a clinical evaluation to determine whether or not sufficient clinical data exist to confirm conformity with the safety and performance requirements of the Essential Requirements

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is not a new requirement, even though the term “clinical evaluation” appears only in the title of Annex X of the MDD and Annex 7 of the AIMDD. This is because the current versions of these Annexes require that the adequacy of clinical data is determined, which means that it must be evaluated. Nonetheless, as discussed previously, the need to do this for all classes of devices has not been clearly understood by all manufacturers.

The revising Directive adds a new Essential Requirement to the MDD and AIMDD. It states that the demonstration of conformity with the Essential Requirements must include a clinical evaluation in accordance with Annex X. In the MDD, this new Essential Requirement is 6a and in the AIMDD it is 5a. This addition removes all doubt regarding the need to conduct a clinical evaluation for all classes of devices.

Expansion of Clinical Evaluation Annex

To fully understand the implications of the revisions relating to clinical evaluation, it is necessary to clearly understand the significant additions made by the revising Directive to the general provisions of the Clinical Evaluation in Annex X of the MDD and in Annex 7 of the AIMDD. The modifications to Annex X of the MDD are listed below; however, readers should review the revised Directives for the full text of the changes. The following changes have been made to Section 1.1 of Annex X:

- The reference to implantable devices and devices in Class III regarding the need to base confirmation of conformity with certain Essential Requirements on clinical data has been removed, as discussed previously
- The Essential Requirement, which states that any undesirable side effect must constitute an acceptable risk when weighed against the intended performance (Section 6 of Annex I), has been added to the list of essential requirements requiring clinical data for demonstrating conformity.
- The term “clinical evaluation” is introduced, and it is specified that any evaluation must follow a defined and methodologically sound procedure based on the evaluations described in Sections 1.1.1, 1.1.2 and 1.1.3 of Annex X.

In the current and revised versions of the Directives, Section 1.1.1 describes the process of basing a clinical evaluation on

relevant scientific literature and Section 1.1.2 indicates that clinical evaluation can be based on the results of all the clinical investigations made. The revising Directive adds Section 1.1.3, which indicates that a clinical evaluation can be based on a critical evaluation of the combined clinical data provided in Sections 1.1.1 and 1.1.2.

In addition to the modification of existing sections and the addition of Section 1.1.3, four important sections have been added to the general provisions of Annex X of the MDD and Annex 7 of the AIMDD. These are:

- The need to perform clinical investigations with implantable devices and devices in Class III unless it is duly justified to rely on existing clinical data.
- The need to document the clinical evaluation and its outcome, and the requirement that this documentation must be included and/or fully referenced in the technical documentation of the device.
- The need to actively update the clinical evaluation and its documentation with data obtained from the postmarket surveillance; where postmarket clinical follow-up as part of the postmarket surveillance plan for the device is not deemed necessary, this conclusion must be duly justified and documented.
- Where demonstration of conformity with essential requirements based on clinical data is not deemed appropriate, the need for adequate justification for any exclusion, and the requirement to base this conclusion 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; the adequacy of demonstration of conformity with the Essential Requirements by performance evaluation, bench testing and preclinical evaluation alone must be duly substantiated.

Other clinical revisions

Part 2 of this article will cover the revisions to the MDD and AIMDD relating to the conduct of clinical investigations, the European database, postmarket clinical follow-up, conformity assessment of clinical data and areas that Notified Bodies are expected to check during their assessment of clinical data. In addition, the revised international standard on clinical investigations with medical devices, useful global harmonisation guidance documents, and suggestions on avoiding problems in complying with the new or clarified requirements will be discussed. ☺

Reference

1. Directive 2007/47/EC can be obtained from the European Commission website: http://ec.europa.eu/enterprise/sectors/medical-devices/index_en.htm.

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