

Revised European Guidance on Clinical Evaluations, Part 1

A significantly revised European guidance document has been published that will dramatically affect how medical device companies address the European clinical evaluation process and how Notified Bodies will assess compliance with clinical evaluation requirements. Part 1 of this two-part article will discuss important principles underlying the approach taken in the guidance. Part 2 will cover the stages of clinical evaluation and the role of the Notified Body in checking this process.

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Requirements for clinical evaluation

The revised European Active Implantable Medical Device Directive (AIMDD) (90/385/EEC) and the Medical Device Directive (MDD) (93/42/EEC) contain an important clarification regarding the need for clinical evaluation. That is, Essential Requirement 5a of the revised AIMDD and 6a of the revised MDD state that demonstration of conformity with the Essential Requirements must include a clinical evaluation. This applies to all devices unless it is concluded that the demonstration of conformity with the Essential Requirements based on clinical data is not deemed appropriate.

If clinical data are not deemed appropriate, manufacturers must comply with section 1.5 of Annex 7 of the revised AIMDD and section 1.1d of Annex X of the revised MDD, which state that “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.” The expanded clinical data and clinical evaluation requirements in the revised Directives are further discussed in a previous article.¹

Increased harmonisation

Europe has taken important actions to promote harmonisation with regard to clinical data requirements. For example, the revisions made to the AIMDD and MDD, which become mandatory



on 21 March 2010, include a new definition for clinical data that is virtually identical to the definition in the Global Harmonisation Task Force (GHTF) guidance document on clinical evidence.² In addition, the revised Directives state that clinical data are sourced from:

- clinical investigation(s) of the device concerned
- 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
- published and/or unpublished reports on other clinical experience →

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→ of the device in question or a similar device for which equivalence to the device in question can be demonstrated.

The inclusion of unpublished reports in the revised Directives as a source of clinical data promotes harmonisation between Europe and the United States (US). This is because unpublished adverse information and a summary of all other unpublished information (whether adverse or supportive) are required by 21 CFR Section 812.27, Report of Prior Investigations, under the US Investigational Device Exemption regulations in 21 CFR Part 812; unpublished data are also required under the US Premarket Approval regulations in 21 CFR 814.

In addition, Europe took another important step in aiding harmonisation of clinical data requirements by using the GHTF guidance document on clinical evaluation³ as a basis for the development of the newly revised European guidance document (MEDDEV) on clinical evaluation.⁴ Readers should obtain the new MEDDEV on clinical evaluation as soon as possible. It is a much more detailed guidance document than the previous version, extending to 46 pages compared with the previous version's 19 pages. The contents of the new guidance document are presented in Table I.

It should be noted that important differences remain between Europe and the US regarding clinical data such as highly specific clinical data and clinical study requirements based on FDA

expectations, which may or may not be described in FDA guidance documents. For this reason, it is wise, where practicable, to obtain an opinion from FDA on the adequacy of clinical data, including the clinical protocol, when clinical studies are to be conducted to generate clinical data in support of a US regulatory submission.

Concepts, principles and process

To ensure that valuable time is not wasted on producing insufficient clinical evaluations, manufacturers need to have a clear understanding of what clinical evaluation is, when it needs to be conducted and why it is important. These questions are covered in the Introduction section of the MEDDEV guidance document. The previous version contained some of this information, but the revised version is much more comprehensive in explaining the basic principles of clinical evaluation.

The Introduction also explains that clinical evaluation is the assessment and analysis of clinical data pertaining to a medical device to verify the clinical safety and performance of that device. It also points out that clinical evaluation is first performed during the conformity assessment process leading to the marketing of the medical device, and that it is an ongoing process conducted throughout the device life cycle. This is an important point because some manufacturers may believe that once they have conducted a clinical evaluation during the conformity assessment process to market the product in Europe, it does not need to be updated as new clinical safety and performance information becomes available from the use of the device.

In the section, "What is the Process?" the Introduction states that to conduct a clinical evaluation, a manufacturer needs to

- identify the Essential Requirements that require support from relevant clinical data
- identify available clinical data relevant to the device and its intended use
- evaluate data in terms of its suitability for establishing the safety and performance of the device
- generate any clinical data needed to address outstanding issues
- bring all the clinical data together to reach conclusions about the clinical safety and performance of the device.

It is further stated that the results of this process are documented in a clinical evaluation report. This clinical evaluation report and the clinical data on which it is based serve as the clinical evidence that supports the marketing of the device. It is this evidence, together with other design verification and validation documentation, device description, labelling, risk analysis and manufacturing information, that are needed to allow a manufacturer to demonstrate conformity with the Essential Requirements and it forms part of the technical documentation of a medical device.

Some readers may find it easier to manage the clinical evaluation process by incorporating the other steps described in the MEDDEV guidance into the list of activities above. These other steps include defining the scope of the clinical evaluation (section 5.1 of the MEDDEV) and performing the activities described in the clinical

TABLE 1: Contents of Clinical Evaluation MEDDEV 2.7.1. Rev.³

Preface	10 The role of the Notified Body in the assessment of clinical evaluation data
1.0 Introduction	10.1 Examination of design dossier
2.0 Scope	10.2 Evaluation as part of the quality system procedure
3.0 References	10.3 Notified Body specific procedure and expertise
4.0 Definitions	Appendices
5.0 General principles of clinical evaluation	A: A possible format for the literature search report
6.0 Sources of data/ documentation used in a clinical evaluation (Stage 1)	B: A possible methodology for documenting the screening and selection of literature within a literature search report
6.1 Data generated through literature search	C: Some examples to assist with the formulation of criteria
6.2 Data generated through clinical experience	D: A possible method of appraisal
6.3 Data from clinical investigations	E: A possible format for a clinical evaluation report
7.0 Appraisal of clinical data (Stage 2)	F: Clinical evaluation checklist for Notified Bodies
8.0 Analysis of the clinical data (Stage 3)	10 The role of the Notified Body in the assessment of clinical evaluation data
9.0 The Clinical Evaluation Report	10.1 Examination of design dossier

evaluation stages (section 5.2 and Figure 1 of the MEDDEV) into one general list of activities. It is advisable that these and other related steps are included in a written procedure on clinical evaluation, which is discussed further in Part 2 of this article.

Essential requirements and clinical evaluation

Some manufacturers do not understand the relationship between clinical evaluation and the Essential Requirements even though the relationship is defined in the medical device Directives. That is, section 1.1 of Annex 7 of the AIMDD and Annex X of the MDD list the Essential Requirements for which conformity as a general rule must be based on clinical data. It is also important to note that conformity to other Essential Requirements, depending on the particular medical device, may also need to be based on clinical data. If the Essential Requirements that need to be supported by clinical data are not properly identified, there is a danger that insufficient, inadequate or even in some cases, unnecessary clinical data may be identified or generated. This can be avoided if the manufacturer, before beginning a clinical evaluation, defines its scope. The scope should be based on the Essential Requirements that need to be addressed from a clinical perspective considering whether any device design features or target treatment populations require special attention; whether data from equivalent devices can be used to support the safety or performance of the device; and the data sources and types of data to be used in the clinical evaluation. →

→ Risk analysis and clinical evaluation

The relationship between risk analysis and clinical evaluation is also a critical issue and is covered in section 5, General Principles of Clinical Evaluation, which discusses the need to define the scope of the clinical evaluation. With regard to design features or target treatment populations requiring special attention, the risk management documents are expected to identify the risks associated with the device and how these risks have been addressed. The clinical evaluation is expected to address the significance of any risks that remain after design risk mitigation strategies have been implemented by the manufacturer. If an appropriate risk analysis has not been performed or is not up-to-date before the clinical evaluation is performed, the clinical evaluation may not sufficiently address relevant device risks.

Clinical evaluation stages

Part 2 of this article will discuss aspects of the advice the guidance provides on how to actually perform a clinical evaluation, the appendices that have been provided and the role of the Notified Bodies in the assessment of clinical evaluation documentation. It will also discuss a checklist in the guidance that Notified Bodies are expected to use or at least take into consideration in their clinical evaluation assessment activities.

References

1. M.E. Donawa, "New European Device Clinical Requirements, Part 1," *European Medical Device Technology*, 1, 1, 16–19 (2010) <http://emdt.co.uk/article/new-efforts-harmonise-clinical-evaluation>
2. Global Harmonisation Task Force, Clinical Evidence (May 2007), www.ghtf.org/sg5/sg5-final.html
3. Global Harmonisation Task Force, Clinical Evaluation (May 2007), www.ghtf.org/sg5/sg5-final.html
4. Clinical Evaluation: A Guide for Manufacturers and Notified Bodies (MEDDEV 2.7.1 Rev.3, December 2009); http://ec.europa.eu/enterprise/sectors/medical-devices/files/meddev2_7_1rev_3_en.pdf

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