

# New Efforts to Harmonise Clinical Evaluation

**Maria Donawa**

Manufacturers wishing to market globally face varying regulatory requirements for assessing and analysing clinical data in support of medical device safety and performance claims. This article discusses the need for harmonising these requirements and two proposed documents developed to address this need.

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## European requirements

Under the European directives for medical devices, as a general rule the confirmation of medical device safety and performance and the evaluation of undesirable side effects must be based on adequate clinical data. Annex X, Clinical Evaluation, of the Medical Device Directive (93/42/EEC), provides options on the manner in which adequate clinical data can be generated. It can be done by compiling relevant scientific literature or by conducting clinical investigations. Annex X also specifies the objectives of clinical investigations, ethical considerations and the essential elements regarding methods that must be used in conducting clinical investigations. Annex 7 of the Active Implantable Medical Device Directive (90/385/EEC) contains similar requirements. This article does not include a discussion of performance evaluation requirements for the In Vitro Diagnostic (IVD) Medical Device Directive (98/79/EC) because the proposed guidance documents discussed in this article exclude IVD products from their scope.

The European harmonised standards for medical device clinical investigations, ISO 14155:2003, Parts 1 and 2, provide detailed guidance on the conduct of clinical investigations. The European guideline, Evaluation of Clinical Data: A Guide for Manufacturers and Notified Bodies (MEDDEV 2.7.1, April 2003) provides additional guidance to manufacturers on the evaluation of clinical data, and guidance to Notified Bodies on reviewing the results of this evaluation.

## US requirements

In the United States (US), Premarket Notification Procedures in Subpart E of 21 Code of Federal Regulations (CFR) Part 807, Establishment Registration and Device Listing for Manufacturers and Initial Importers of Devices, list the type of clinical information that must be included in a 510(k) submission. The Premarket Approval (PMA) regulations, in 21 CFR Part 814, which apply to devices in the highest risk category, Class III, provide detailed information on clinical data that must be included in the PMA application.

For example, section 814.20(b)(8)(i) requires the PMA application to include a bibliography of all published reports, whether adverse or supportive known to the applicant concerning the safety or effectiveness of the device. FDA specifies that these reports are in addition to, and not the same as, the data and information on laboratory studies and clinical investigations conducted by the applicant. Section 814.20(b)(8)(ii) requires an identification, discussion and analysis of any other data, information or report relevant to an evaluation of the safety and effectiveness of the device known to the applicant from any source, foreign or domestic. This includes information derived from investigations other than those proposed in the application and from commercial marketing experience.

## Need for harmonisation

There are important differences between European and the US clinical data requirements. The current versions of →



### Dr Maria E. Donawa

physician, pathologist and pharmacist with 25 years' regulatory experience, worked with the US FDA before becoming President of Donawa Consulting, an international consultancy firm, which provides clinical research, quality management system, regulatory affairs, and European Authorised Representative services to medical technology companies.

→ the European directives for medical devices describe two types of clinical data that can be used to support medical device safety and performance claims. These are clinical data based on a compilation of relevant scientific literature or on clinical investigations. Therefore, the directives do not explicitly mention the use of clinical data that may be obtained from other sources such as unpublished data on clinical experience of the device in question or a similar device for complying with clinical data requirements. This is an important difference from the US where this type of information is expected to be supplied to FDA.

In addition, in Europe only general information is available regarding the development and analysis of clinical data; however, more specific guidance documents are likely to be developed in future. In contrast, FDA has developed guidance documents for some products that describe the medical device safety and performance aspects that FDA considers important and for which clinical data should be supplied.

For example, FDA has developed a guidance document for certain types of cardiovascular intravascular filters.<sup>1</sup> Under US regulations, the types of cardiovascular device for which the guidance was developed are in Class II and require the submission of a 510(k) or premarket notification, which is a much less stringent regulatory process compared with the PMA process. However, clinical data are sometimes needed for 510(k) submissions. In this guidance document, FDA lists the complications that should be identified and analysed during the course of the clinical investigation, if one becomes necessary, for example, complications during filter insertion or recurrent pulmonary embolism. Therefore, manufacturers wishing to market these and many other types of medical devices in the US must identify US requirements for clinical data, which may be much more detailed than those found in European regulatory and guidance documents.

**Table I:** The proposed definitions of clinical investigation, clinical data, clinical evaluation and clinical evidence.

Term	Proposed definition
Clinical investigation	Any systematic investigation or study in or on one or more human subjects, undertaken to assess the safety and/or performance of a medical device
Clinical data	Safety and/or performance information that are generated from the clinical use of a medical device
Clinical evaluation	The assessment and analysis of clinical data pertaining to a medical device to verify the clinical safety and performance of the device when used as intended by the manufacturer
Clinical evidence	The clinical data and the clinical evaluation report pertaining to a medical device

### GHTF Study Group 5

The Global Harmonisation Task Force (GHTF) is a voluntary group of representatives from national regulatory authorities and industry.<sup>2</sup> The purpose of GHTF is to encourage convergence in regulatory practices relating to ensuring the safety, effectiveness/performance and quality of medical devices. This is accomplished by developing and disseminating harmonised guidance documents on basic regulatory practices, which can then be adopted and implemented by member national regulatory authorities.

GHTF Study Group 5 was established in June 2004 to promote convergence of regulatory requirements for evidence of the clinical safety and performance of medical devices. The group has developed and issued two proposed guidance documents, one on definitions and concepts related to clinical evidence<sup>3</sup> and the other on clinical evaluation.<sup>4</sup> Comments will be accepted on these documents until 17 January 2007.

### Guidance on definitions and concepts

GHTF's proposed document, Clinical Evidence, Key Definitions and Concepts, provides definitions of clinical investigation, clinical data, clinical evaluation and clinical evidence (see Table I). This proposed document is important because it not only provides a basis for harmonising important terms, but also lays the foundation for understanding the GHTF's proposed document on clinical evaluation, which is discussed below.

Each definition is accompanied by a short explanation that provides additional information on the use of the term. For example, the definition of clinical evidence points out that clinical evidence is an important component of the technical documentation of a medical device. This evidence, together with other design verification and validation documentation, device description, labelling, risk analysis and manufacturing information are needed to allow a manufacturer to demonstrate conformity with the Essential Principles, which are described in the GHTF document.<sup>5</sup> The Essential Principles are analogous to the Essential Requirements of the European directives, which served as a model for the development of these principles.

A flow chart at the end of the proposed document titled, Overview of Process For Data Generation and Clinical Evaluation, suggests the steps to take to generate clinical evidence for inclusion in the technical documentation of a medical device.

### Guidance on clinical evaluation

GHTF's proposed document, Clinical Evaluation, provides guidance on how to conduct and document the clinical evaluation of a medical device for demonstrating conformity with clinical data requirements before placing the device on the market, or to support its continued marketing. Readers will find that the information contained in this document is different in important ways from that in the European guidance document, Evaluation of Clinical →

→ Data (MEDDEV 2.7.1). For example, the GHTF document provides an introductory section that explains what clinical evaluation is and why it is important, it describes the process of conducting a clinical evaluation and comments on the level of detail that it should contain. The latter is particularly useful because of the significant diversity in the types of medical device technology, the history and experience with the technology and the related risks.

The document states that many medical devices are developed or modified by incremental innovation, therefore, they are not completely novel. In these cases, it is often possible to establish clinical evidence based on the clinical experience and literature reports of the safety and performance of comparable devices, thereby reducing the need to conduct clinical investigations for the device in question. The document adds that it may also be possible to comply with recognised standards to satisfy clinical evidence requirements for devices based on technologies with well-established safety and performance characteristics. In addition, the proposed document contains guidance on

- the general principles of clinical evaluation such as the need to define the scope of the clinical evaluation before it is undertaken and a description of the stages of a clinical evaluation
- how to identify relevant clinical data to be used in a clinical evaluation
- how to evaluate and integrate clinical data into a summary
- how to document a clinical evaluation in a clinical evaluation report.

In contrast, the MEDDEV guidance includes a mixture of the type of clinical evaluation documentation that should be developed together with the type of evaluation of clinical data that Notified Bodies should conduct. In fact, the purpose of the MEDDEV document is to provide guidance to manufacturers on reviewing and analysing clinical data and what is expected; and guidance to Notified Bodies when reviewing the evaluation conducted by manufacturers. However, some users of both documents find that the proposed GHTF document is easier to use because it concentrates primarily on how to conduct clinical evaluation and provides practical help on how to accomplish this task.

### Closing the gap

This article has discussed some of the differences between the US and European requirements for documented clinical evaluation. However, the gap between US and European clinical data requirements will narrow if the proposed revisions of the Medical Device Directive, which are currently available on the European Commission website,<sup>6</sup> are adopted. These include important new requirements related to clinical data and the need to document clinical evaluation. In the meantime, prudent manufacturers who already understand the importance of these

activities will use the proposed GHTF document to implement or improve internal procedures for ensuring that clinical data and evaluation are managed and documented properly. Even though this document will most likely change, it already contains usable information.

### Reference

1. Downloadable from [www.fda.gov/cdrh/ode/24.pdf](http://www.fda.gov/cdrh/ode/24.pdf)
2. [www.ghrf.org](http://www.ghrf.org)
3. Study Group 5, GHTF, Proposed Document, Clinical Evidence, Key Definitions and Concepts, 26 April 2006, [www.ghrf.org/sg5/sg5-proposed.html](http://www.ghrf.org/sg5/sg5-proposed.html)
4. Study Group 5, GHTF, Proposed Document, Clinical Evaluation, 26 April 2006, [www.ghrf.org/sg5/sg5-proposed.html](http://www.ghrf.org/sg5/sg5-proposed.html)
5. Study Group 1, GHTF, Essential Principles of Safety & Performance of Medical Devices, 21 July 2005
6. Downloadable from [http://ec.europa.eu/enterprise/medical\\_devices/revision\\_mdd\\_en.htm](http://ec.europa.eu/enterprise/medical_devices/revision_mdd_en.htm) **mdt**

### Maria E. Donawa

Donawa Consulting,  
Piazza Albania 10, I-00153 Rome, Italy,  
tel. +39 06 578 2665,  
e-mail: [medonawa@donawa.com](mailto:medonawa@donawa.com) [www.donawa.com](http://www.donawa.com)