

# New European Device Clinical Requirements: Part 2

Part 1<sup>1</sup> of this two-part article discussed the requirements on clinical data and evaluation that will come into effect on 21 March 2010. Part 2 covers the revisions of requirements on clinical investigations, the European database, postmarket clinical follow up and conformity assessment of clinical data. It also discusses the revised standard on device clinical investigations and useful global harmonisation guidance documents and suggests how to avoid problems in complying with the new or clarified requirements.

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## Clinical investigation revisions

Several changes and clarifications have been made to the Medical Device Directive (MDD) (93/42/EEC) and the Active Implantable Medical Device Directive (AIMDD) (90/385/EEC) by the Revising Directive<sup>2</sup> with regard to clinical investigations. As mentioned in Part 1,<sup>1</sup> where this article discusses the amendments made to the MDD, analogous amendments have also been made to the AIMDD.

Paragraph 1 of Article 15, Clinical Investigation, of the current version of the MDD states that the procedure referred to in Annex VIII, Statement Concerning Devices for Special Purposes, must be followed when notifying Member States of clinical investigations that will be conducted in their territories. A revision to paragraph 1 clarifies that the notification must be made by means of the statement described in Section 2.2 of Annex VIII. This Annex has also been revised and is discussed later.

A clarification has been made to paragraph 2 of Article 15 of the MDD, which specifies requirements concerning the authorisation of devices in Class III and implantable and long-term invasive devices in Classes IIa and IIb. The current version states that Member States may authorise the start of a clinical investigation before the expiry of 60 days, if the relevant ethics committee has issued a favourable opinion on the programme of investigation in question. The revised version states that this opinion must include a review of the clinical investigation plan.

The current and revised versions of paragraph 6 of Article 15 of the MDD state that Member States shall, if necessary, take the



appropriate steps to ensure public health and public policy; however, the revised MDD includes two new requirements concerning the information shared by Member States. Where a clinical investigation is refused or halted by a Member State, the Member State must communicate its decision and the grounds for the decision to all other Member States and the European Commission. In addition, when a Member State has called for a significant modification or temporary interruption of a clinical investigation, the Member State must inform the other Member States concerned about its actions and the grounds for the actions taken.

The revision of paragraph 7 of Article 15 of the MDD will require additional action to be taken by manufacturers. The current and revised versions of the MDD require that the manufacturer or his authorised representative keep the report, which contains a critical evaluation of the clinical data collected during the clinical investigation and referred to in point 2.3.7 of Annex X, at the disposal of the Competent Authorities. Under the revision of this



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paragraph, the manufacturer or his authorised representative will be required to notify the Member States concerned of the end of the clinical investigation, with a justification if it is terminated early. If early termination is on safety grounds, the notification must be communicated to all Member States and the European Commission.

It should also be noted that a revision to Article 14a, European Databank, of the MDD will require Member States to enter data relating to clinical investigations into the European databank. This revision will facilitate Member States' communication regarding the surveillance of multicentred studies conducted in various Member States. The databank is not yet functioning; the revising Directive requires it to function no later than 5 September 2012.

### Devices for special purposes

Annex VIII of the MDD requires that a statement containing specified information is drawn up for custom-made devices and for devices intended for clinical investigations. This is not a new requirement; however, the information that needs to be included under the revised Annex has been expanded. This new information includes the investigator's brochure, confirmation of insurance of subjects and the documents used to obtain informed consent. In addition, a statement indicating whether or not the device incorporates, as an integral part, a medicinal substance or human blood derivative is required.

This is an important revision because it specifies the information that will need to be provided to Member States during the process of notifying Member States of clinical investigations of non-CE-marked devices intended to be conducted within their territories.

### Postmarket clinical follow-up

The conformity assessment procedures described in Annexes II, V and VI of the MDD have been revised and require manufacturers to include the provisions referred to in Annex X relating to the establishment of procedures for reviewing postmarket experience. The relevant Annex X provisions are in the new section 1.1c of Annex X, which states that clinical evaluation and its documentation must be actively updated with data obtained from postmarket surveillance. This new section also states that 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.

Section 5.2 of Annex II of the MDD requires that the manufacturer authorises the Notified Body to perform all the necessary inspections. Thus, the manufacturer must supply the Notified Body with relevant information such as documentation on the quality system. This section has been revised and the information that must be supplied to the Notified Body includes not only the design data that were previously described such as the results of analyses and →

→ calculations, but also preclinical and clinical evaluation, postmarket clinical follow-up plan and the results of the postmarket clinical follow-up, if applicable.

As a result of these revisions, manufacturers will need to develop careful justification for not conducting postmarket clinical follow-up studies. Manufacturers should also be prepared for evaluations of compliance with postmarket clinical follow-up requirements during Notified Body assessment and quality system audit activities. The European guidance document, Guidelines on Post Market Clinical Follow-up<sup>3</sup> has been developed as a guide to manufacturers and Notified Bodies concerning compliance with postmarket surveillance requirements by incorporating postmarket clinical follow-up studies where appropriate. Manufacturers should review this document, but should also be aware of a global harmonisation guidance document on the same subject, which is discussed later.

### Notified Body assessments

Where Notified Bodies are involved in the CE-marking process, they will need to check compliance with the new clinical data, evaluation and investigation requirements when they perform their assessment activities. To help prepare manufacturers for this process, some Notified Bodies are conducting seminars or offering other means of providing information on their expectations. As a minimum, manufacturers should check with their Notified Bodies to ensure that they understand how the Notified Body will interpret the new requirements and assess compliance.

Manufacturers should review the European guidance document, Evaluation of Clinical Data: A Guide for Manufacturers and Notified Bodies.<sup>4</sup> This document provides guidance on the role of the Notified Body in assessing clinical evaluation data, which is required under the current versions of the Directives. This document is undergoing an important revision process to incorporate guidance on complying with the revised clinical evaluation requirements and the areas that should be assessed by Notified Bodies during their technical documentation and quality system audits. Readers should check the European Commission's website for news on when this document will be issued. Until the revised European guidance document is available, it is strongly recommended that manufacturers consider the advice provided in the global harmonisation documents on clinical evidence and clinical evaluation, which are discussed later.

### Revised clinical study standard

Any manufacturer wishing to conduct medical device clinical studies in Europe needs to understand the importance of conforming to EN ISO 14155:2003 Quality Standard for Clinical Investigation of Medical Devices for Human Subjects. This is the European harmonised standard, which means that manufacturers can use this standard to demonstrate compliance with the requirements for clinical investigations specified in the medical device Directives. The standard specifies requirements for the proper design, conduct and documentation of medical device clinical investigations. Part 1 of

the standard provides general requirements, and Part 2 describes the contents of clinical investigation plans.

Manufacturers should be aware that the standard is currently undergoing a significant revision. For example, its proposed new title is "Clinical Investigation of Medical Devices for Human Subjects, Good Clinical Practices" and Parts 1 and 2 will be combined into a single standard. In addition, it will have a new structure, inconsistencies in the previous version will have been resolved and there will be some harmonisation, where appropriate, with international principles of good clinical practices. At this time,

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however, the revised ISO 14155 is available only as a draft international standard (DIS), which has been issued for review and comment only, and is therefore subject to change before final adoption.

It is hoped that a final draft international standard (FDIS) will be available before 21 March 2010, when compliance with the revisions to the Directives become mandatory. If this occurs, many manufacturers may decide to use the FDIS because that version is unlikely to undergo important changes during the final voting process prior to the final standard being published. Manufacturers are advised to consult with their Notified Bodies before making this decision.

### Harmonised guidance documents


The Global Harmonisation Task Force (GHTF)<sup>5</sup> is a voluntary international association supporting the adoption of a global medical device regulatory model. GHTF consists of medical device regulatory authorities and industry representatives; a steering committee; five study groups; and representatives from Europe, United States, Canada, Japan, Australia and other countries. Information on the GHTF can be found at [www.ghrf.org](http://www.ghrf.org). Study Group 5, Clinical Safety/Performance, is responsible for promoting convergence of regulatory requirements for evidence of the clinical safety and performance of medical devices. The study group has developed two final documents: Clinical Evaluation (SG5/N2R8:2007) and Clinical Evidence (SG5/N1R8:2007) and two proposed documents, Clinical Investigations (SG5(PD)N3R7) and Postmarket Clinical Follow-Up (SG5(PD)N4R7).<sup>6</sup>

Readers attempting to gain a better understanding of how they should comply with the new European clinical requirements are encouraged to review these documents, but keep in mind the specific European regulatory requirements, including relevant terminology. For example, GHTF documents refer to compliance with Essential Principles, whereas the legal requirement in Europe

is compliance with the Essential Requirements. In spite of this difference, the documents were developed to support harmonised clinical regulatory requirements, including European requirements. Thus, readers should be aware that the revision of the MEDDEV guidance document on clinical evaluation, discussed previously, is based on the contents of the GHTF guidance document with the addition of specific guidance on the role of Notified Bodies. It is likely that the GHTF guidance documents on clinical investigations and postmarket clinical follow-up will play a similar role in the development or revision of European MEDDEV documents related to these two areas.

### Avoiding compliance problems

How should manufacturers ensure compliance with the new or clarified European clinical requirements? A comprehensive programme should be in place that includes as a minimum the review of the revised Directives, awareness of any European national variations where clinical investigations are to be conducted, contact with the Notified Body to obtain information on its expectations, development of relevant procedures and policies that are consistent with the new requirements, review of applicable European and GHTF guidance documents, in-house training, and a careful check on compliance. Prudent companies will have already

begun this process to ensure that valuable time and resources will not need to be devoted to resolving compliance problems identified by Notified Bodies or surveillance programmes that may be initiated by Member States. 

### References

1. M.E. Donawa, "New European Device Clinical Requirements: Part 1," *European Medical Device Technology*, 1, 1, 17–19 (2009).
2. Directive 2007/47/EC can be obtained from: [ec.europa.eu/enterprise/sectors/medical-devices/index\\_en.htm](http://ec.europa.eu/enterprise/sectors/medical-devices/index_en.htm)
3. Guidelines on Post Market Clinical Follow-up (MEDDEV 2.12-2, May 2004) can be obtained from [ec.europa.eu/enterprise/sectors/medical-devices/files/meddev/2\\_12-2\\_05-2004\\_en.pdf](http://ec.europa.eu/enterprise/sectors/medical-devices/files/meddev/2_12-2_05-2004_en.pdf)
4. Evaluation of Clinical Data: A Guide for Manufacturers and Notified Bodies (MEDDEV 2.7.1, April 2003) can be obtained from [ec.europa.eu/enterprise/sectors/medical-devices/files/meddev/2\\_7\\_en.pdf](http://ec.europa.eu/enterprise/sectors/medical-devices/files/meddev/2_7_en.pdf)
5. Information on the GHTF can be found at [www.ghtf.org](http://www.ghtf.org)
6. These documents can be found at [www.ghtf.org/sg5](http://www.ghtf.org/sg5)

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