

Revised European Guidance on Clinical Evaluations, Part 2

Part 1 of this two-part article discussed important principles underlying the approach taken in the new European guidance on clinical evaluation.¹ Part 2 covers advice provided in the guidance on how to perform a clinical evaluation, guidance appendices, the role of the Notified Body in assessing clinical evaluation, a clinical evaluation assessment checklist, and the need for written procedures.

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Steps preceding a clinical evaluation

Recently, a medical device company set about initiating activities for ensuring compliance with the newly clarified European requirements for clinical evaluation. The company took many of the steps described in the new European guidance document on clinical evaluation;² however, certain important actions were not taken. The Essential Requirements that needed to be supported by clinical data had not been identified, there was no analysis of device risks remaining after risk mitigation, which should have been addressed by the clinical evaluation, and the scope of the clinical evaluation had not been defined. As a result, it was not clear whether the clinical data adequately supported the Essential Requirements that needed to be addressed from a clinical perspective.

To avoid this shortcoming, particular attention should be paid to section 5.1 of the guidance, which discusses the need to define the scope of the clinical evaluation before it is undertaken. The scope should be based on the Essential Requirements that need to be supported by clinical data. For devices falling under the Medical Device Directive (MDD) (93/42/EEC), these are, at a minimum, the Essential Requirements in sections 1, 3 and 6 of Annex I. For devices subject to the Active Implantable Medical Device Directive (90/385/EEC), they are the Essential Requirements in sections 1, 2 and 5 of Annex 1.

Another important step that should be taken early in the clinical evaluation process is the determination of whether or not data from equivalent devices can be used to support the safety and/or performance of the device in question. Section 5.1 describes the criteria that should be used to establish equivalence between the device in question and equivalent devices. The guidance states that



equivalence should be based on the intended use, together with the technical and biological characteristics of the device. Readers should refer to the guidance for a full discussion of the criteria for equivalency.

Clinical evaluation process

Once the scope of the clinical evaluation has been defined, the clinical evaluation process can be considered to consist of three stages:

- Stage 1: Identification of clinical data from literature searching, clinical experience and/or clinical investigation; conformity to harmonised performance standards may be sufficient to demonstrate compliance to relevant Essential Requirements
- Stage 2: Appraisal of individual data sets for suitability and the



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contribution of results to the demonstration of performance and safety

- Stage 3: Analysis of relevant data, including, strength of overall evidence and conclusions about performance and safety.

Each stage is covered in separate sections of the guidance. Stage 1 is discussed in section 6, Stage 2 in section 7, and Stage 3 in section 8. The clinical evaluation report is discussed in section 9.

Data from scientific literature

Section 6.1, Data Generated through Literature Search, discusses the possibility of generating data through literature searching, which may relate directly to the device in question or to equivalent devices. Readers will be interested to know that the guidance states that a literature search protocol should be developed before the search is conducted. This will be an important new activity for most medical device companies. This protocol should describe the search strategy and methods and include:

- the sources of data that will be used and a justification for selecting them
- the extent of any searches of scientific literature databases (the database search strategy)
- the selection/criteria to be applied to published literature and justification for choosing them
- strategies for addressing the potential for duplication of data

across multiple publications.

After the literature search has been completed, a literature search report should be developed, which provides the results of the search. The report should include a copy of the protocol and any deviations from the protocol should be documented. A possible format for the literature search report is in Appendix A of the guidance. Copies of the literature citations retrieved from each database search should be attached to the report. The guidance also advises that a flow chart and associated tables showing how all citations were assessed for suitability for inclusion in the clinical evaluation should also be attached to the report. An example of this type of flow chart is provided in Appendix B.

Data from clinical experience

Section 6.2, Data Generated through Clinical Experience, provides information on a clinical data source that is particularly useful for low-risk devices based on long standing, well-characterised technology and, therefore, unlikely to be the subject of reporting in the scientific literature or a clinical investigation. This is important because many devices fall into this latter category. This section discusses clinical data generated from actual clinical use, which does not include clinical studies, and which may relate to the device in question or equivalent devices. This type of clinical data may include:

- manufacturer-generated postmarket surveillance reports, registries or cohort studies, which may contain unpublished long-term safety and performance data
- adverse events databases held by the manufacturer or regulatory authorities
- data for the device in question generated from individual patients under compassionate usage programmes prior to marketing of the device
- details of clinically relevant field corrective actions such as recalls, notifications or hazard alerts.

Guidance is also provided on the contents of postmarket surveillance reports and postmarket data about adverse events.

Data from clinical investigations

Section 6.3, Data from Clinical Investigations, provides guidance on the generation of clinical data from clinical investigations performed by, or on behalf of, a manufacturer specifically for the purposes of premarket conformity assessment. The guidance lists the clinical investigation documentation/data that should be used in the clinical evaluation, which may include:

- the clinical investigation plan
- any clinical investigation plan amendments and the rationale for those changes
- the relevant Ethics Committee(s)' documentation, opinion(s) and comments for each investigation site, including a copy of the approved informed consent form(s) and patient information documents
- case report forms, monitoring and audit records
- regulatory authority approvals and associated correspondence as required by applicable regulations
- the signed and dated final report.

Manufacturers need to pay particular attention to the need to assess whether or not the conduct of the investigation was in accordance with the current applicable ethical standards. Clinical investigations that do not comply with applicable ethical standards or regulations should be rejected. The reasons for rejection of the investigation should be noted in the report.

Appraisal and analysis

Section 7, Appraisal of Clinical Data, describes Stage 2 of the clinical evaluation process. Each piece of data should be appraised to determine its suitability to address questions about the device and its contribution to demonstrating the safety and performance of the device. Appendix C provides examples of questions to ask that should assist with the formulation of criteria for appraising different types of data sets, including randomised control studies, cohort studies, case-control studies and case series. An example of a method of data appraisal is provided in Appendix D.

Section 8, Analysis of the Clinical Data, provides guidance on Stage 3 of the clinical evaluation process. The purpose of this stage is to determine if the appraised data sets available for a medical device collectively demonstrate the clinical performance and safety

of the device in relation to its intended use.

As a final step, the evaluator of the data should determine whether or not the data from the selected sources show that the device performs as intended by the manufacturer and does not pose any undue safety concerns to the recipient or end-user. In addition, any remaining risks associated with the use of the device must be acceptable when weighed against the benefits to the patient.

Other factors that should be taken into account include the number of patients exposed to the device, the type and adequacy of patient monitoring, the number and severity of adverse events, the adequacy of the estimation of associated risk for each identified hazard, and the severity and natural history of the condition being diagnosed or treated. The analysis should also consider the availability of alternative diagnostic modalities or treatments and the current standard of care.

Clinical evaluation report

Once the clinical evaluation process is completed, a clinical evaluation report should be developed to describe the scope and context of the evaluation, the clinical data, the appraisal and analysis stages and the conclusions concerning the safety and performance of the device in question. The guidance states that this report should contain sufficient information to be read as a stand-alone document by an independent party such as a regulatory authority or Notified Body. A suggested format for the clinical evaluation report is located at Appendix E.

If the clinical evaluation report concludes that clinical evidence is insufficient to be able to declare conformity with the Essential Requirements, additional data will need to be generated. It may therefore be necessary to conduct a clinical study or broaden the scope of literature searching to address the deficiency.

Notified Body role and checklist

Section 10, The Role of the Notified Body in the Assessment of Clinical Evaluation Data, provides guidance to Notified Bodies on the assessment of clinical evaluations. It also states that it can be useful as best practice guidance for national Competent Authorities in their market surveillance activities. This is an extremely important section for manufacturers because it will help them to prepare not only for Notified Body assessments of clinical evaluation documentation, but also for Competent Authority surveillance checks, in particular, with regard to Class I devices, which do not require Notified Body involvement.

This section describes the different roles that a Notified Body has depending on the classification of the device and the conformity assessment procedure. For example, if a manufacturer selects Annex II as the conformity assessment procedure for the MDD, the Notified Body conducts an audit as part of the quality system approval procedure. In this case, the Notified Body is expected to assess the manufacturer's procedure for clinical evaluation. In addition, as part of the representative sampling of devices for review of their technical documentation, the Notified Body verifies the

acceptability of the clinical evaluation data presented for Class IIa and Class IIb devices in accordance with the criteria outlined in section 10 of the guidance document.

Section 10.1 provides guidance on how the Notified Body should examine clinical evaluation documentation submitted in a design dossier or type examination dossier. This section also draws attention to Appendix F of the guidance, which provides a checklist that the Notified Body should use when assessing clinical evaluation documentation. The checklist is detailed and extends to 12 pages. The first section covers the evaluation of a manufacturer's justification for demonstrating conformity to relevant Essential Requirements without clinical data. Each of the additional five sections contains multiple aspects of the clinical evaluation documentation that is to be checked.

Section 10.2 covers the examination of clinical evaluation procedures and documentation as part of the quality system, including the review of written procedures and the technical documentation of Class IIa and Class IIb devices. The Notified Body should assess the clinical evaluation documentation of at least one representative sample of each device subcategory for Class IIa devices and at least one representative sample of each generic device group of Class IIb devices. Additional representative samples will need to be assessed as part of surveillance audits.

It is important to note that this section states that when performing the assessment on samples of a manufacturer's clinical evaluation, the Notified Body should follow the steps indicated in section 10.1 of the guidance, which includes the use of the assessment checklist.

Need for written procedures

Considering the European requirements for clinical evaluation and the actions that manufacturers are expected to take to fulfill these requirements, it is clear that written procedures are needed to facilitate this process and provide consistency in the actions taken. Section 10.2.1, Review of the Manufacturer's Procedures, advises that the Notified Body should assess the establishment, maintenance and application of the documented procedures for the evaluation of clinical data as part of the review of the manufacturer's quality system.

Readers are advised to review the guidance document for the complete description of areas that the procedures should cover, however, briefly stated, this includes:

- assignment of responsibilities to suitably qualified persons
- integration of clinical evaluation into the quality system
- standard operating procedures to assure proper planning, conduct, evaluation, control and documentation of the various steps of the clinical evaluation process
- document control
- identification and evaluation of undesirable side effects and of clinical performance of the device as part of the manufacturer's documented risk analysis, based on both favourable and unfavourable clinical data identified during the clinical evaluation process.

Clinical evaluation readiness

Prudent manufacturers will ensure that the underlying European requirements in the medical device Directives are clearly understood, take time to carefully examine the new guidance on clinical evaluation, decide how the requirements should be met for their particular devices, develop appropriate clinical evaluation procedures, and if necessary, contact the Notified Body or other regulatory support to clarify any doubts regarding the clinical evaluation process. In this manner, useful and compliant clinical evaluation documentation can be developed, which reduces the risk of an insufficient or excessive approach to this important time and resource intensive process.

References

1. M.E. Donawa, "Revised European Guidance on Clinical Evaluations, Part 1," *European Medical Device Technology*, 1, 3, 16–20 (2010), emdt.co.uk/article/revised-european-guidance-clinical-evaluations-part-1. Revised European Guidance on Clinical Evaluations, Part 1,.
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