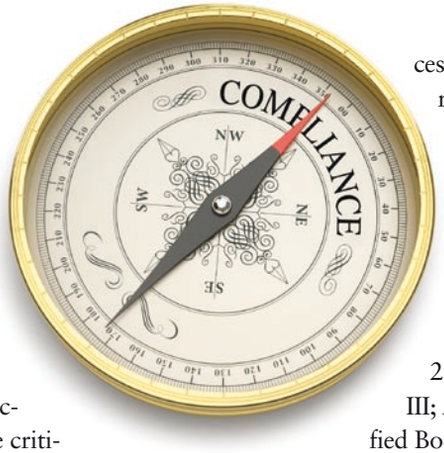
Guidance to Notified Bodies on Checking Clinical Evaluations

There are two European documents that contain guidance for assisting Notified Bodies in conducting an effective assessment of clinical data and clinical evaluations. One is better known than the other. This article discusses both documents and their usefulness in ensuring acceptable clinical evaluation documentation.



THE EUROPEAN GUIDANCE document (MEDDEV) on clinical evaluation,[1] which was discussed in a previous two-part article,[2, 3] provides comprehensive guidance on processes for complying with European clinical evaluation requirements for medical devices regulated under the Medical Devices Directive (MDD; 93/42/EEC) and Active Implantable Medical Devices Directive (AIMDD; 90/385/EEC).

The MEDDEV is directed not only to manufacturers, but also to Notified Bodies because of the critical role that they play in the assessment and verification of manufacturer-provided clinical evaluations to support demonstration of conformity of a device with the essential requirements of the relevant directive. With this in mind, Section 10 of the MEDDEV, "The role of the Notified Body in the assessment of clinical evaluation data," provides detailed guidance to Notified Bodies on the assessment of clinical evaluations provided by medical device manufacturers as part of the technical documentation or design or type-examination dossier. The guidance also points out that this section might be useful as best practice guidance for national Competent Authorities in their market surveillance activities.

For these reasons, the MEDDEV guidance is useful to manufacturers not only because it describes a process for conducting and documenting clinical evaluations, but also because it contains guidance on the assessment of clinical evaluations. If manufacturers check their own procedures and documentation using the assessment guidance, they will be better prepared for Notified Body assessments or possible market surveillance checks conducted by Competent Authorities. Avoiding nonconformities during these assessments can help to prevent delays in the CE marking process or the expenditure of precious resources in responding to Competent Authority questions on identified clinical evaluation–related nonconformities.

Examination of design or type examination dossiers

In Section 10.1 of the MEDDEV, "Examination of a Design Dossier (Annex II.4; Annex 2.4) or of a Type Examination Dossier (Annex III; Annex 3)," the guidance explains that the Notified Body examines the submitted clinical evaluation documentation; verifies the manufacturer's identification, appraisal, analysis and assessment of that data; and validates the conclusions drawn by the manufacturer.

Section 10.1.1, "Decision-making by the Notified Body," lists the types of activities that should be verified and assessed for adequacy during the evaluation of clinical data submitted by the manufacturer. For example, the Notified Body is expected to determine whether or not the manufacturer has adequately supplied clinical evaluation documentation (as referenced in sections 5 to 9 of the MEDDEV) and performed other activities.

Readers should review the guidance for the full list of activities that Notified Bodies are expected to check, which can be used by manufacturers to better prepare for the Notified Body assessment.

Section 10.1.1 also points out that Notified Body assessment will typically include the following aspects of the manufacturer's clinical evaluation:

- appraisal to determine suitability and any limitations of the data presented to address the essential requirements, in particular relating to the safety and performance of the device as outlined in section 7 of the MEDDEV;

Dr Maria E. Donawa

A physician, pathologist and pharmacist with nearly 30 years' regulatory experience, Maria E. Donawa worked with US FDA before becoming President of what is now Donawa Lifescience Consulting, a full service European CRO and international consultancy company that provides regulatory, quality and European Authorised Representative services to life science companies.

- presence of adequate procedures (according to sections 5 to 9 of the MEDDEV)
- the validity of any justification given;
- the listing, characterisation and proof of the clinical performance of the device intended by the manufacturer and the expected benefits for the defined patient group(s);
- the use of harmonised standards.

Once again, readers should review the entire list of aspects that Notified Bodies are expected to check and use the list in their preparation for assessment.

Evaluation as part of quality system procedures

Section 10.2, "Evaluation as Part of Quality System Related Procedures (Annex II.3 of Directive 1993/42/EEC)," of the MEDDEV provides guidance on the review of the manufacturer's procedures and review of the technical documentation. These sections also should be used in checking that procedures adequately address clinical evaluation. Although the MEDDEV is not legally binding and neither the MDD nor AIMDD specifically require standard operating procedures (SOPs) for clinical evaluation, it is highly advisable that companies develop SOPs to cover clinical evaluation activities and documentation.

Section 10.2.1, "Review of the manufacturer's procedure," states that the Notified Body shall, as part of the review of the manufacturer's quality system, assess the establishment, maintenance and application of the manufacturer's documented procedures for the evaluation of clinical data. This should cover activities such as:

- the proper assignment of responsibilities to suitably qualified persons involved in the clinical evaluation;
- the integration of clinical evaluation into the quality system;
- SOPs to ensure proper planning, conduct, evaluation, control and documentation of the various phases of clinical evaluation, including the need to update the clinical evaluation based upon postmarket clinical data;
- Document control as part of overall documentation of procedures, reporting, qualifications and technical documentation/design dossier(s);
- identification and evaluation of undesirable side effects of clinical performance(s).

Section 10.2.2, "Review of the technical documentation of representative samples," provides guidance on the assessment of technical documentation for Class IIa and Class IIb devices, which must be on a representative basis. The guidance states that clinical evaluation data should be assessed by the Notified Body for at least one representative sample of each device subcategory for Class IIa devices and of each generic device group for Class IIb devices. Further representative samples should be assessed as part of the annual surveillance assessment cycle. An important point is made in this

section: assessment of representative samples includes assessment of clinical evaluation data according to the criteria outlined in the MEDDEV rather than a simple confirmation that the manufacturer has a clinical evaluation procedure in place. In this regard, the guidance states that when performing the assessment on samples of a manufacturer's clinical evaluation, the Notified Body will follow the steps indicated in section 10.1 of MEDDEV.

Clinical evaluation checklist for Notified Bodies

Section 10.1 of the MEDDEV, discussed previously, points out that Appendix F of the MEDDEV includes a checklist to be used by the Notified Body for assessing clinical evaluation data. Although this section provides guidance related to the assessment of clinical evaluation data in design or type-examination dossiers, it is expected that the checklist will be used for assessing clinical evaluations not only as part of design or type-examination dossiers, but also as part of the technical documentation for lower risk devices.

The checklist items are divided into the following main categories, which consist of a series of questions:

- conformity without clinical data, which includes questions related to the adequate justification of demonstrating conformity with essential requirements not based on clinical data;
- clinical evaluation, general;
- clinical investigation route;
- clinical literature data;
- postmarket clinical follow up;
- Notified Body decision making.

There are more than 80 items requiring a response—yes, no and not applicable—thus the checklist is quite comprehensive. There is also a space for comments beside each checklist item. An example of some of the items in Section 3 of the checklist, "Clinical literature data," in the "Methodology" subsection are:

- A critical evaluation of relevant scientific literature has been presented;
- A search protocol for the identification, selection, collation and review of relevant publications should be written;
- The objective of the literature review should be clearly defined;
- The types of studies that are relevant to the objective of the literature review should be specified;
- Data should be taken from recognised scientific publications. Unpublished data should also be taken into account in order to avoid publication bias.

Manufacturers should use the MEDDEV checklist to assess whether they have fully understood clinical evaluation requirements, all relevant clinical evaluation-related activities have been performed, and any necessary clinical evaluation documentation has been developed and is easily retrievable. This will provide an important measure of assurance that clinical evaluation requirements have been understood and met, but the checklist in Appendix F does not cover all types of questions that Notified Bodies could ask during their clinical evaluation assessments. Important additional questions are posed in the guidance document discussed below.

Notified Body Operations Group checklist

The Notified Body Operations Group (NBOG) was established in July 2000 by European member states and the European Commission in response to concerns that the performance of Notified Bodies in the medical device sector, and the Designating Authorities responsible for them, was variable and inconsistent. As a result, the NBOG terms of reference are to improve the overall performance of Notified Bodies in the medical devices sector by primarily identifying and promulgating examples of best practices to be adopted by both Notified Bodies and those organisations responsible for their designation and control. NBOG has developed several best practice guides including a checklist for Designating Authorities to use when performing assessments of a Notified Body's capability for assessing clinical evaluation documents and clinical data presented in support of conformity with the MDD or AIMDD.

The document is divided into section A, "Resource Requirements," and section B, "Process Requirements." Based upon its purpose, it could be concluded that the document is not particularly useful to manufacturers in checking their compliance with clinical evaluation requirements; however, section B, "Process Requirements," is very useful. It includes questions that Notified Bodies should cover in their assessment of clinical evaluation, but that are not included in the MEDDEV guidance document. This is easy to understand in that the NBOG best practice document was developed after the issuance of the MEDDEV.

A detailed discussion of each question included in the NBOG document that is not included in the MEDDEV is beyond the scope of this article. However, listed below are some examples of the questions:

- Does the NB request details of any ongoing, terminated and completed clinical investigations, including samples of final reports during surveillance audits of manufacturers?
- Does the NB check whether the sponsor has fulfilled any conditions before starting the clinical investigation?
- Does the NB request reports on postmarket surveillance or postmarket clinical follow-up data from the manufacturer for specific products (e.g., when identification of emerging risks/evaluation of long-term safety and performance is critical)?

In some cases, a similar question is included in the MEDDEV, but covered differently or in more detail in the NBOG document. For example, does the NB procedure assess the manufacturer's selection of and justification for assigning personnel to conduct the evaluation based on:

- Qualifications and documented experience?
- Knowledge of the device technology and its application?
- Knowledge of research methodology (clinical investigation design and biostatistics)?
- Diagnosis and management of the conditions intended to be treated or diagnosed by the device?

While most questions in the NBOG document concern issues also identified in the MEDDEV, prudent manufacturers will review the NBOG best practice document to supplement and improve their efforts for complying with clinical evaluation requirements.

References

1. *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/meddev/2_7_1rev_3_en.pdf
2. M.E. Donawa, "Revised European Guidance on Clinical Evaluations, Part 1," *European Medical Device Technology*, **1**, 3, 16–20 (2010), www.emdt.co.uk/article/revised-european-guidance-clinical-evaluations-part-1
3. M.E. Donawa, "Revised European Guidance on Clinical Evaluations, Part 2," *European Medical Device Technology*, **1**, 4, 16–20 (2010), www.emdt.co.uk/article/revised-european-guidance-clinical-evaluations-part-2
4. Checklist for audit of Notified Body's review of Clinical Data/Clinical Evaluation, *NBOG Best Practice Guide* (March 2010); www.nbog.eu/resources/NBOG_CL_2010_1.doc

Maria E. Donawa,
Donawa Lifescience Consulting, Piazza Albania 10, I-00153 Rome, Italy
tel. +39 0 6578 2665 | medonawa@donawa.com | www.donawa.com