CLINICAL EVALUATION OF MEDICAL DEVICES
RE-EVALUATING THEIR IMPORTANCE
UNDER A NEW REGULATORY Spotlight
Introduction

Every medical device sold into Europe, irrespective of its classification, must have an up-to-date Clinical Evaluation Report (CER) as part of its Technical File. Although guidance is available on the requirements for clinical evaluation, it is not comprehensive. This lack of clarity has led to varying approaches to the CER process by manufacturers and Notified Bodies (NBs), resulting in uncertainty for manufacturers as to whether their CER procedures will be considered compliant and their medical devices adequately supported.

The 2007 amendment to the Medical Device Directive (MDD) and supporting standards have attempted to address known shortcomings in the availability and use of clinical data to support medical devices. However, recent scandals – such as Poly Implant Prostheses’ use of cheaper, industrial-grade silicone in breast implants and toxic debris from metal-on-metal hip implants – have highlighted weaknesses in terms of the MDD’s content and, more notably, its implementation. NBs (and consequently manufacturers and their CERs) are now coming under increasing scrutiny, which will increase further with the introduction of the new Medical Device Regulation (MDR). For any manufacturer wishing to introduce or maintain their medical device on the European market, the importance of understanding and correctly implementing the requirements for clinical evaluation has become paramount. All manufacturers, including those with previously successful CERs, should revisit their procedures to ensure there are no unpleasant surprises during their NB’s next review of their Technical File.

To support efforts by medical device manufacturers to ensure compliance in this area, this white paper will:

+ Highlight common sources of non-compliance
+ Clarify requirements and address gaps in clinical evaluation guidance
+ Help manufacturers attain compliance and prepare for future regulatory changes
Regulatory Background

After the introduction of the three MDDs in the 1990s, the successful implementation of the “New Approach” has been subject to ongoing review and refinement. In 2002, the Medical Device Experts Group published a report highlighting concerns relating to conformity assessment. Specific feedback was that manufacturers did not always have data available, NBs did not sufficiently verify the adequacy of clinical data provided with respect to characteristics and performances of the device, and MDD wording could lead to doubts on interpretation.

Attempts were made to address these issues in 2003 with guidance in the form of MEDDEV 2.7.1 “Clinical Evaluation: A Guide for Manufacturers and Notified Bodies.” The subsequent amendment to the Medical Device Directive (93/42/EEC) in 2007 (2007/47/EC) added further obligations. MEDDEV 2.7.1 was updated in 2009 to reflect the Global Harmonization Task Force (GHTF) document on “Clinical Evaluation” and the requirement for a more robust and systematic approach. The current guidance is MEDDEV 2.7.1 Rev. 3.

Despite these efforts, the same three issues identified in the 2002 report with regard to conformity assessment and clinical data remain today. This is further highlighted by recent well-publicized safety alerts, including concerns with metal-on-metal hip implants, silicone breast implants, transvaginal mesh, and IUD medical devices. Consequently, NBs are under increased pressure to improve their performance in terms of safeguarding public safety.

In 2012, the Joint Plan for Immediate Action reinforced the role of NBs under the current legislation, requiring increased use of unannounced inspections and restriction of their activities to devices where they have proven competence. In addition, the new MDR is currently undergoing review. It has already been agreed that there will be increased focus on improved conformity assessments by NBs, and these assessments will include requirements relating to their in-house expertise. As a result of these changes, NBs are likely to continue work to improve their processes and skill sets – and more frequent and rigorous assessments can now be expected. The new regulation will also attempt to avoid differences in interpretation by providing clarity in terms of definitions and expectations with regard to clinical data. Although not expected to come into force until 2018 at the earliest, it is possible that, where ambiguity exists, NBs will turn to the new regulation for guidance on what may have been intended. Manufacturers will need to ensure they are clear on the current requirements and that they keep abreast of the progress and themes of the MDR.

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Requirements for Clinical Evaluation

When a medical device is placed on the market, the manufacturer must have demonstrated through the use of appropriate conformity assessment procedures that the device complies with the relevant Essential Requirements (ERs). From a clinical perspective, it is expected that the manufacturer will demonstrate that the device achieves its intended performance and that the known and foreseeable risks, and any adverse events, are minimized and acceptable when weighed against the benefits of the intended use, and that any claims made about the device’s performance and safety are supported by suitable evidence. It is here where the clinical evaluation plays an important role supporting this crucial compliance and risk management activity. Moreover, every device requires one to meet the regulatory requirements of the MDD, as you will see noted in Annex I.

Clinical Evaluation: Not a One-Time Isolated Activity

Clinical evaluation is defined as the assessment and analysis of clinical data pertaining to a medical device in order to verify its clinical safety and performance when used as intended. Two key elements are often inadequately addressed:

+ **It is an ongoing activity** conducted throughout the life cycle of the device.
+ **It is not a stand-alone activity** – clinical evaluation, risk management, and post-market surveillance (PMS) activities are by necessity interlinked and cannot be conducted effectively in isolation.

Any clinical evaluation of a new device will be based on limited clinical data for the device itself. Although the evaluation is based on the best data available at that time, the truest indication of safety and performance will only be obtained once the device is in clinical use. As additional clinical use data becomes available, increased clarity on the risk/benefit profile of the device can be obtained, particularly with regard to:

+ Real world use
+ Unforeseen risks
+ Rare complications
Under the MDD, manufacturers are required to proactively conduct PMS as part of their Quality Management System (QMS) and the outputs are an integral part of the clinical evaluation. As more data becomes available, the CER must be updated periodically to take account of new information, thereby ensuring that the risk/benefit assessment remains up-to-date and acceptable, and the safety and performance claims for the device continue to be supported.

Similarly, risk management and clinical evaluation are closely linked in a two-way relationship. Risk management activities should identify risks that need to be addressed by the CER and PMS. In return, clinical evaluation (and PMS) can help identify, quantify, and modify previously identified risks. Manufacturers need to ensure that their QMS procedures account for the interrelationship of these three activities, and that triggers for the update of CERs are in place.

The Clinical Evaluation Process

In brief, the steps of the clinical evaluation process are as follows:
The Clinical Evaluation Report (CER)

The CER documents the entire clinical evaluation process. It is a stand-alone document that provides the NB or other reviewer with adequate information to assess the appropriateness of the methodology, included data, and conclusions. Report formats may vary, but some general points relating to common errors are provided below:

- As discussed, the CEP, search histories, and included data need to be appended to the CER. The CER and appendices are stored in the Technical File – forming both the clinical evidence and part of the technical documentation for the device.
- There needs to be sufficient information provided to enable the assessor to understand the device and its application, but it should be concise and limited to relevant data. The clinical data and evaluation should form the bulk of the main body of the CER.
- The CER format suggested in MEDDEV 2.7.1 does not refer to all elements to be included and does not facilitate effective evaluation of different data sources and aspects to be considered. This template should be adapted before use. It is advisable to ensure that the elements discussed within the guideline – including the NB Checklist in its Appendix – and within this document are addressed within the CER template used.
- Content must be adequately and accurately referenced. This includes applied regulations and standards, clinical background of a device or general statements, Technical File/PMS/risk management documentation, and previous CER versions.
- The CER should be signed and dated by the author and by appropriately authorized reviewers. The author’s CV and/or justification with regard to his or her appropriate qualification should be included.
- The CER must have a strong conclusion, summarizing the findings of the evaluation and clearly stating the conclusions with regard to each of the elements. Ensure the MEDDEV 2.7.1 elements (see below) are incorporated and also identify any additional actions to be taken with regard to risk management or the generation of additional data.

Tips for Writing CER Conclusions

- Clearly outline the conclusions reached about safety and performance of the device with respect to its intended use.
- State whether the risks identified in the risk management documentation have been addressed by the clinical data.
- For each proposed clinical indication, state whether:
  - the clinical evidence demonstrates conformity with relevant Essential Requirements;
  - the performance and safety of the device as claimed have been established; and
  - the risks associated with the use of the device are acceptable when weighed against the benefits to the patient.
Clinical Evaluation – Resource Challenges and Potential Solutions

Time
Many manufacturers underestimate the time taken to complete a CER. Conducted systematically, a CER can take up to three months to finalize - although it will take less time for an update. Time can be a major problem for manufacturers of all sizes, particularly if there are many devices requiring a new, updated, or revised CER (or if they are trying to catch up on CER requirements for multiple Class I devices). Nevertheless, with unannounced inspections from NBs becoming the norm, medical device companies need to ensure that time is no longer a hindrance to compliance.

Expertise
The CER must be completed by qualified, accredited individuals. Authors are expected to possess knowledge of the device and therapy area as well as knowledge of research methodology and systematic/critical review skills. Expertise and familiarity with regard to the CER process itself are also important to avoid non-compliance and overcome gaps in the guidance. Where experienced researchers/CER writers are not available in-house, it is essential that manufacturers develop or procure appropriate expertise.

There are a number of steps manufacturers can take that will help:

Develop Internal/QMS Procedures: Developing an understanding of all the inputs to the clinical evaluation, particularly from internal sources (for example, product information, PMS, and risk management data) and implementing associated procedures will ensure that the required information is available and can be obtained in the correct format and at the right time. Regulatory and QMS consultancy services may be employed to obtain related advice and assistance in process mapping.

Develop CER Procedures: Developing an effective standard operating procedure (SOP) with detailed templates and standard text will allow evaluators to consistently follow the correct process without recreating the wheel each time and therefore save time. These can be developed internally or with help from outside compliance experts.

Training: Ensuring that CER writers/stakeholders are trained on the CER process and are not relying solely on guidance will remove the likelihood of time-consuming revisions during the production phase or after a NB review. Developing in-house expertise is essential, whether for writing or for reviewing outsourced CERs. Training courses are available on clinical evaluation and also on other aspects of research methodology.

Team Approach: Allocating elements of the process to different (appropriately trained) internal and/or external personnel will shorten the time to completion of an individual CER. For instance, data extraction requires a narrower skill set and can be done by someone other than the CER author. Considering areas of expertise can save time and improve quality – often the author is required to collate data that would more effectively be produced by others, such as ED product data/justification, which would be better provided by the technical team.
Adequate Resourcing: Allocating dedicated staff for this time-consuming activity may help avoid backlogs due to conflicting workloads. Many companies with additional resource requirements insource or outsource the preparation of CERs, and many consultancies offer this service. CERs can often be completed according to the client’s or the consultant’s procedures. The main benefits are in terms of clinical evaluation expertise and a proven track record, and often a team of people is available to help achieve shorter timelines. Combining external expertise and resources with internal processes for providing timely data inputs means that, with a partnership approach to maintaining compliance, organizations never need be out of step with NBs and regulatory requirements.

Conclusion

With the constantly changing regulatory landscape and increased pressure on Notified Bodies, manufacturers must be prepared for the increasing scrutiny of their CERs and heightened expectations with regard to the appropriate use of clinical data to support their devices. Five years after the amendment to the Medical Device Directive was implemented, there are still gaps in the implementation of requirements. This paper shows how, with the right knowledge, resources, and processes, medical device companies can use a new approach to CERs to forge a successful pathway to meet regulatory changes and market needs.
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