MEETING THE EU’S CLINICAL EVALUATION REQUIREMENTS FOR MEDICAL DEVICES
The clinical evaluation of a medical device is intended to critically evaluate the clinical benefits of a given device against the potential risks it poses to patients. As such, clinical evaluations are an essential element of the risk management process applicable to medical devices under regulatory approval schemes in most major markets around the world. At the same time, more rigorous requirements for clinical evaluations under the European Union's (EU's) new medical device regulation (MDR) are expected to extend the application of clinical evaluation requirements to a broader range of medical device manufacturers, while also increasing the regulatory compliance complexity for all.

The latest revision of the European Commission guidance document on clinical evaluations of medical devices, MEDDEV 2.7/1 revision 4, provides device manufacturers with an effective roadmap for achieving compliance with clinical evaluation requirements. Published in June 2016, the revised guidance document is specifically applicable to medical devices and active implantable medical devices, and is already being adopted by EU Notified Bodies in their assessment of clinical evaluations.

This UL white paper discusses the specifics of the new and modified aspects of the latest revision of MEDDEV 2.7/1, and how this guidance document can assist medical device manufacturers in achieving compliance with the EU's new clinical evaluation requirements. Beginning with a summary of the role of clinical evaluations in the approval of medical devices, the white paper also reviews the anticipated changes in the EU’s MDR, with special attention to the changes in the requirements for clinical evaluations. The white paper then discusses the importance of the MEDDEV guidance document as well as the changes and clarifications to the guidance reflected in the 2016 revision. The white paper concludes with recommendations for device manufacturers on effectively addressing clinical evaluation requirements.
The Importance of Clinical Evaluations

Medical device regulations around the world generally require manufacturers of medical devices to validate claims regarding the safety and performance of their products. The goal of the clinical evaluation process is to collect and continually analyze relevant clinical data to help ensure that a device performs as intended under anticipated use conditions, and that the nature and probability of any risks are identified and determined to be acceptable when weighed against the benefits.

A clinical evaluation is not a discrete event but part of an ongoing process that is conducted throughout the entire lifecycle of a medical device, from initial product design and development, through regulatory review and approval and, finally, during actual use after a device has been placed on the market. This process allows manufacturers to provide regulators as well as the public with ongoing assurances regarding the safety and efficacy of their devices as well as continued compliance with applicable requirements.

The scope and depth of a clinical evaluation required for a given medical device depends on several factors, including the level of risk posed by the device and the specific regulatory requirements of a jurisdiction. In general, however, a clinical evaluation process includes the following steps:

1. Identify the regulatory requirements for which relevant clinical data is required;
2. Identify any currently available third-party clinical data that may be relevant to a device and its intended use;
3. Assess the extent to which available data is suitable to establish the safety and performance of the device;
4. As required, conduct clinical investigations in accordance with the requirements of ISO 14155 to generate additional clinical data; and
5. Evaluate all data to determine whether it conclusively supports claims of the device’s safety and performance.

This process and the resulting data are documented in a clinical evaluation report (CER). The CER, along with other documentation on the design verification and validation of the device, risk analysis, manufacturing and labeling information, is part of the required technical documentation for a medical device, and is used by regulatory officials and testing agencies to assess compliance with the requirements in force in a given jurisdiction.

The Changing Landscape in EU Medical Device Requirements

For more than two decades, the framework regulating medical devices in the EU has been based on two separate directives, one addressing requirements for medical devices (93/42/EEC, also referred to as the Medical Device Directive, or MDD), and the second setting requirements for active implantable medical devices (90/385/EEC, also referred to as the Active Implantable Medical Device Directive, or AIMDD). (In vitro diagnostic medical devices, which are outside
the scope of this white paper, are regulated by a third directive, 98/79/EC.) However, as part of a sweeping effort in 2012 to address identified deficits in its approach to the regulation of medical devices, the EU Commission published a proposed regulation (EU No 2012/0266) for medical devices and active implantable medical devices.

The EU’s MDR introduces several important changes to the requirements applicable to medical devices, including an expanded scope of regulated devices, greater oversight of EU Notified Bodies and unannounced audits of suppliers. In the area of clinical evaluations, the MDR includes more rigorous clinical investigation requirements, on a par with those applicable in the EU to medicinal products. Specifically, the regulations establish more exacting requirements and limitations on the use of available clinical data for so-called equivalent devices as part of the clinical evaluation process. This change is expected to require extensive comparative experimental and analytical testing to demonstrate that a particular device is “equivalent” to a device under evaluation, forcing more manufacturers to conduct their own clinical studies in support of the conformity assessment process.

The MDR also requires device manufacturers to conduct post-market surveillance (PMS) and post-market clinical follow-up (PMCF) studies to assess and evaluate actual safety and performance of a device in widespread use. Device manufacturers are required to update their CERs upon receipt of any information received through PMS or PMCF activities that may change the current evaluation. In the absence of the receipt of any such information, manufacturers of high-risk medical devices must update the CER at least annually, while CERs covering other devices must be updated every two to five years.

The final MDR is expected to be published sometime in 2017, and device manufacturers will have three years from the date of the MDR’s publication to meet the new requirements. Unlike previous directives applicable to medical devices which relied on legislation and regulation in individual EU Member States to take effect, the MDR will have the immediate force of law throughout the EU and will not be subject to interpretation by national authorities.
What is MEDDEV 2.7/1?

Officially titled “Clinical Evaluation: A Guide for Manufacturers and Notified Bodies,” MEDDEV 2.7/1 is a guidance document published by the EU Commission and developed in consultation with Commission officials, national regulators and representatives from the medical device industry. As its title indicates, the guidance is intended to offer a common approach that can be applied by both medical device manufacturers and Notified Body personnel in the development and review of clinical evaluations to assess the safety and performance of medical devices as required by EU directives and regulations.

The first edition of MEDDEV 2.7/1 was originally published in April 2003 and was based on similar clinical evaluation guidelines first developed by the former Global Harmonization Task Force (GHTF). The guidance has been subsequently revised and updated on several occasions to reflect changes in EU legislation applicable to medical devices, as well as more recent protocols in clinical evaluation practices. The most recent revision of MEDDEV 2.7/1, revision 4, was published in June 2016.

Similar to guidance documents from regulators in other countries and jurisdictions, the approach to the conduct of clinical evaluations presented in MEDDEV 2.7/1 is not legally binding, and device manufacturers can adopt alternative approaches that are based on sound, scientific principles that address the EU’s essential requirements for medical devices. Nonetheless, because MEDDEV 2.7/1 is being widely adopted by EU Notified Bodies, device manufacturers who follow the approach to clinical evaluations detailed in the guidance may experience fewer challenges during the conformity assessment evaluation of new device applications.

Changes and Clarifications in MEDDEV 2.7/1 Revision 4

The scope of MEDDEV 2.7/1 revision 4 represents a significant expansion from revision 3 of the guidance published in December 2009. The overall length of the guidance has increased by nearly 50 percent, from 46 pages to 65 pages. But more than mere length, revision 4 provides significantly more detail on each aspect of the clinical evaluation process. Rather than introducing new requirements, MEDDEV 2.7/1 revision 4 includes more explicit guidance than revision 3 regarding the clinical evaluation process, as well as more specific examples intended to simplify their application.

Importantly, MEDDEV 2.7/1 revision 4 serves to bring its recommended clinical evaluation practices into closer alignment with the requirements of the EU’s MDR. Specific examples of the changes and clarifications in MEDDEV 2.7/1 revision 4 include:
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- **More specifically defined stages for the clinical evaluation process** - Clauses 7 through 11 of the revised guidance describe the scope and stages of the clinical evaluation process in far greater detail than earlier versions of the guidance.

- **Tighter restrictions on the use of “equivalent” devices** - Consistent with Annex X of the MDD and Annex 7 of the AIMDD, Appendix A1 of MEDDEV 2.7/1 revision 4 (“Demonstration of equivalence”) now mandates an assessment of clinical, technical and biological characteristics of equivalent devices, and prescribes how those characteristics should be evaluated and documented.

- **Greater emphasis on scientific validity of data** - Clause 9 (“Appraisal of pertinent data”) details specific considerations to assess the applicability of clinical evaluation data, including methodological quality, scientific validity, relevance and weight.

- **Specific protocols for literature search and review** - Similarly, Appendix A5 (“Literature search and literature review protocol, key elements”) prescribes methods for the conduct of searches of clinical evaluation literature prepared by third-parties, and methods for evaluating their validity.

- **New minimum requirements for parties conducting clinical evaluations** - Clause 6.4 (“Who should perform the clinical evaluation?”) stipulates the minimum level of expertise and experience for those involved in the authoring or evaluating a CER. This is a new requirement in MEDDEV 2.7/1 revision 4.

- **Stricter oversight for PMS and PMCF activities** - Appendix A12 (“Activities of notified bodies”) requires Notified Bodies to review a manufacturer’s PMS and PMCF activities and determine their adequacy consistent with any risk identified in the CER.

- **Modified frequency of clinical evaluation updates** - Again, reflecting the requirements of the upcoming MDR, Clause 6.2.3 (“Updating the clinical evaluation”) requires that manufacturers of high-risk devices update the CER at least annually, while CERs for devices that carry little or no risk must be updated every two to five years. CER updates are also required when post-market data from PMS or PMCF activities indicate significant changes in the safety or performance profile of a device.
Transition Considerations and Recommendations for Device Manufacturers

As a guidance document, MEDDEV 2.7/1 revision 4 does not have a defined implementation timetable, and its adoption by EU Notified Bodies is likely to occur over the next year. At the same time, except for new requirements for parties conducting clinical evaluations, MEDDEV 2.7/1 revision 4 is generally consistent with prior editions of the guidance regarding the overall framework and principle requirements for clinical evaluations. And, as previously noted, MEDDEV 2.7/1 revision 4 provides important details on clinical evaluation practices that are consistent with the requirements of the forthcoming EU’s MDR. (A further revision of MEDDEV 2.7/1 can be expected once the new MDR has been published, but changes are likely to be limited to the inclusion of references to the MDR.)

For these reasons, the process of aligning existing clinical evaluation processes and procedures with those in the revised MEDDEV 2.7/1 is likely to represent an incremental undertaking for experienced manufacturers that have the requisite resources to address these changes. However, the majority of companies in the medical device industry consist of small and medium-sized entities that often lack the resident expertise to conduct a thorough and comprehensive clinical evaluation of new medical devices consistent with the requirements of the EU’s MDD, the AIMDD or the forthcoming MDR.

In addition, testing organizations that served as authorized Notified Bodies under the EU’s medical device directives are currently being evaluated by regulators for renotation under the MDR. In the short term at least, this process will almost certainly result in fewer Notified Bodies available to evaluate medical devices. As a result, there may well be increased expectations on the part of the remaining Notified Bodies for device manufacturers to adopt standardized practices for clinical evaluations such as those detailed in MEDDEV 2.7/1 revision 4.

Accordingly, medical device manufacturers should consider taking the several steps to help ensure that their clinical evaluation procedures reflect the requirements of the EU’s MDD, the AIMD and the MEDDEV 2.7/1 guidance, as well as the expectations of EU Notified Bodies. First, manufacturers should study the clinical evaluation requirements for medical devices as presented in MEDDEV 2.7/1 revision 4. The extent of detail and helpful examples and checklists in the guidance can serve as a useful primer on the new requirements and provide a roadmap for implementing a clinical evaluation process consistent with those requirements.

Second, device manufacturers should conduct a gap analysis to identify those areas where their current clinical evaluation practices do not meet the requirements in latest revision of MEDDEV 2.7/1. This exercise is essential in determining the amount of work and time required to bring existing clinical evaluation practices into compliance with the guidance and the MDD and AIMDD, and the forthcoming MDR.
Finally, manufacturers should consider outsourcing some or all aspects of the clinical evaluation process to experienced third-parties who have the requisite knowledge and expertise in the conformity assessment for medical devices. The expense of outside expertise is often offset by a more efficient and timely conformity assessment process, and the ability to bring new medical devices to market more quickly.

Summary and Conclusion

Once published, the EU's new MDR will set significant new requirements for the approval of medical devices in the EU, including more rigorous requirements for the clinical evaluation process. The latest revision of the EU’s MEDDEV 2.7/1 provides authoritative guidance on implementing and maintaining a clinical evaluation process consistent with the requirements of the MDD and the AIMDD, as well as the new MDR, and compliance with the guidance may well become a de facto requirement for Notified Body approval.

To avoid delays in achieving market access in 2017 and beyond, medical device manufacturers should begin work now to integrate the new clinical evaluation requirements into their existing processes and systems. Device manufacturers should also consider the use of an independent and experienced third-party that can fully address the new clinical evaluation requirements, thereby helping to bring new and advanced medical devices to market more quickly and more profitably.

For additional information about UL’s advisory services in the clinical evaluation of medical devices, contact ULMedicalSolutions@ul.com, or visit MedicalSolutions.ul.com.