# How Will Proposed Changes to European Regulation Affect Clinical Data Requirements?

Uncertainty looms as a plethora of proposals and amendments threaten to alter the European medical device regulatory landscape.

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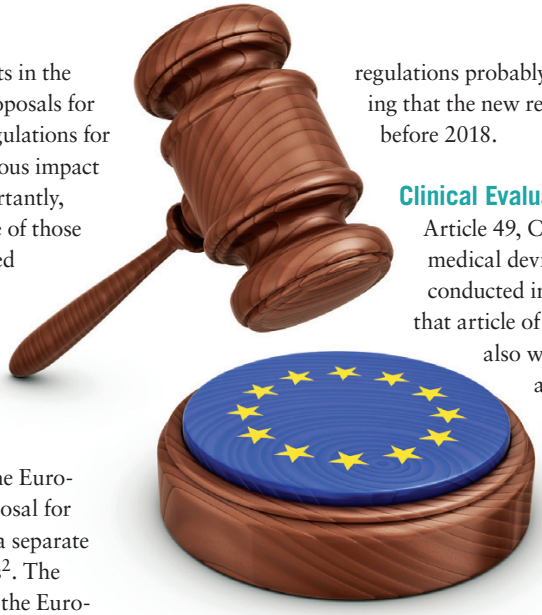

New clinical data requirements in the European Commission's proposals for the revision of European regulations for medical devices will have an enormous impact on all involved parties—most importantly, patients. This article discusses some of those requirements, including the proposed amendments from the European Parliament.

European regulation of medical devices, including in vitro diagnostic (IVD) devices, is undergoing significant revision. On 26 September 2012, the European Commission published a proposal for regulation of medical devices[1] and a separate proposed regulation of IVD devices[2]. The proposed regulations are subject to the European ordinary legislature procedure, which requires examination and adoption by the European Parliament (EP) and Council of the European Union (Council).

On 22 October 2013, the EP voted to accept 347 amendments to the European Commission's proposal for medical devices and 254 amendments for IVD devices[3]. This was not, however, a formal legislative vote; instead, the formal vote was held on 2 April 2014, which resulted in the EP adoption of the text of 22 October 2013. This action closed first reading of the ordinary legislature procedure, requiring that the adopted text be forwarded to the Council, the Commission, and national parliaments.

EP elections, however, will be held 22 to 25 May 2014, which means that newly elected EP members will need time to familiarize themselves with both proposals. In addition, the Council must complete work on its own position on the Commission proposals and EP amendments. Considering the most likely scenario, the proposed regulations probably will not be adopted before late 2015, meaning that the new requirements are unlikely to become mandatory before 2018.

## Clinical Evaluation

Article 49, Clinical evaluation of the proposed regulation for medical devices, specifies that clinical evaluations must be conducted in accordance with the principles established in that article of the proposed regulation for medical devices and also with Part A of Annex XIII, Clinical Evaluation and Postmarket Clinical Follow-Up. As in the current Medical Devices Directives, a clinical evaluation may be based on a critical evaluation of the scientific literature of equivalent devices, a critical evaluation of the results of clinical investigations, or a critical evaluation of the combined clinical data from both sources.

Part A of Annex XIII outlines how to conduct a clinical evaluation, clearly based upon the European guidance document on clinical evaluations (MEDDEV 2.7.1 Rev. 3). The European Commission's proposal is consistent with clinical evaluation requirements in the MDD and AIMDD. This proposal would allow manufacturers to argue that conformity with the general safety and performance requirements based upon clinical data is not necessary. In this case, they would need to duly justify conformity with the same requirements based upon the results of nonclinical testing methods alone. Such an exemption is usually applicable only for low-risk devices.

Unfortunately, the EP has taken issue with this approach, and EP amendment 172 stipulates that this exemption must be subject to prior approval by the competent authority. But the suggestion that prior approval should be given by competent authorities with generally limited resources seems disproportionate, if not unrealistic.

Articles 50 through 60 and Annex XIV of the proposed regulation for medical devices specify the requirements for conducting clinical investigations for regulatory purposes. According to paragraph 1 of Article 50, one of the purposes for a clinical investigation is, "to verify that devices achieve the intended benefits to the patient as specified by the manufacturer."

In contrast, EP amendment 175 states that the purpose is, "to verify the clinical safety and efficacy of the device, including the intended benefits to the patient, when used for the intended purpose, in the target population and in accordance with the instructions for use."

Thus, the EP has introduced a requirement for efficacy into the European medical device regulatory system, which, since its inception, has been based upon essential requirements for safety and performance, where device-related benefits must outweigh any risks of use. It should be noted that no definition for "efficacy" has been included in the EP text as if there were only one meaning of the term, which is clearly not the case.

## Proposed Streamlined Process

Article 51, Application for Clinical Investigations, specifies that the sponsor must obtain a single identification number for the clinical investigation from an electronic system, and use this number to register the clinical investigation. According to the Article, there is no stipulation that the approval process requires the favorable approval of an ethics committee, which is demanded under the current MDD and AIMDD. This would be a significant change from current requirements concerning the approval process for conducting a premarket clinical investigation. Instead, there is a requirement that at least one person whose primary area of interest is nonscientific must be taken into account in the assessment process, and the view of at least one patient must also be taken into consideration.

This is an attempt to align the medical device clinical investigation approval process with the Commission's Proposal for a regulation on clinical trials for medicinal products[4], which would allow Member States to define the national process for the approval of clinical studies. The members of the EP indicate disagreement with this approach as they specified in amendment 181 the requirement to involve an independent ethics committee in the approval process.

## Temporary Halt or Study Termination

Article 57 specifies the timelines in which sponsors need to inform Member States of a temporary halt of a clinical investigation on safety grounds, the end of a clinical investigation, or early termination. The Commission's proposal requires the sponsor to notify each Member State concerned, providing a justification in the event of early termination. EP amendment 189 adds a reason for this notification: "So that all Member States can inform sponsors conducting similar clinical investigations at the same time within the Union of the results of that clinical investigation." This would necessitate a determination presumably by the Member State of what constitutes a similar investigation. Any perceived benefits of this EP proposal clearly must be evaluated against the resources needed for implementation.

### Clinical Investigation Study Design

Chapter II of Annex XIV, Documentation regarding the application for clinical investigation, contains a comprehensive list of information that needs to be included in a clinical investigation application. For example, subparagraph 1.11 states that a summary of the Clinical Investigation Plan (CIP) must be included that describes, among other elements, the design of the investigation, such as a controlled and/or randomised study.

EP amendment 340 adds the following to the Commission proposal text: "As randomised controlled investigations usually generate a higher level of evidence for clinical efficacy and safety, the use of any other design or study has to be justified. Also, the choice of the control intervention shall be justified. Both justifications shall be provided by independent experts with the necessary qualifications and expertise."

The EP appears not to have considered that, in many cases, a randomised controlled study design may not be feasible or ethical when studying a medical device. Such a study design should be considered an option with clear potential advantages. But a requirement limiting medical device clinical investigations to this design further underscores the apparent lack of medical device expertise within the EP.

### Postmarket Clinical Follow-Up (PMCF)

The proposed regulations also clarify and strengthen requirements for PMCF. For example, paragraph 6 of Article 8, General obligations of the manufacturer, specifies that manufacturers must develop a postmarket surveillance plan, which must set out the process for collecting, recording and investigating complaints and reports from healthcare professionals, patients or users on suspected incidents related to a device, in addition to meeting other requirements.

The Article further stipulates that the postmarket surveillance plan must include a plan for PMCF in accordance with Part B of Annex XIII. EP amendment 330 would require manufacturers to make all clinical data collected as part of a PMCF accessible to health professionals. Amendment 331 would require PMCF studies to be registered in the electronic system on vigilance referred to in Article 62 of the proposed regulation.

EP amendment 332 would require that the PMCF evaluation report, as discussed in paragraph 3 of Part B of Annex XIII, is sent periodically to the concerned Member States. In addition, it would require that, for all Class III devices, a third party or external expert review the same report under the principles of highest scientific competence and impartiality. This proposed amendment will need to be carefully evaluated to determine whether its benefits justify the additional associated time and costs.

## EU Process for Technical Legislation

This article addressed only one aspect—clinical data—of the proposed regulation for medical devices. But a review of the remaining proposed EP amendments may lead some to conclude that the process of revising such important regulatory requirements has left much to be desired and is breathtaking in its shortcomings.

To name just a few flaws, the current legislative process has clearly failed to ensure that only those with requisite knowledge and expertise have provided the most input into the proposed amendments, and it has clearly failed to keep political influence to an absolute minimum. Unfortunately, we have to live with the current system and hope for the best. In this respect, it is welcomed that the Council is taking all the time it needs in an effort to ensure that the new regulations are reasonable, constitute an improvement over the current system, will not discourage the introduction of beneficial medical technology in Europe, and will be successfully implemented.

The European Commission's proposals for medical devices and IVDs, combined, totaled nearly 400 pages with 138 recitals or introductory statements, 187 articles, and 30 annexes; more than 600 amendments were proposed by the EP. The EP elections will be held in May, and newly elected members, potentially having even less knowledge of the proposed regulations, will then become involved in the legislative process as well. The importance of the work that still needs to be done, together with its associated challenges under the European legislative process, cannot be overstated.

## References


1. Proposal for a Regulation of the European Parliament and of the Council on medical devices, and amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009; http://ec.europa.eu/health/medical-devices/files/revision_docs/proposal_2012_542_en.pdf
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