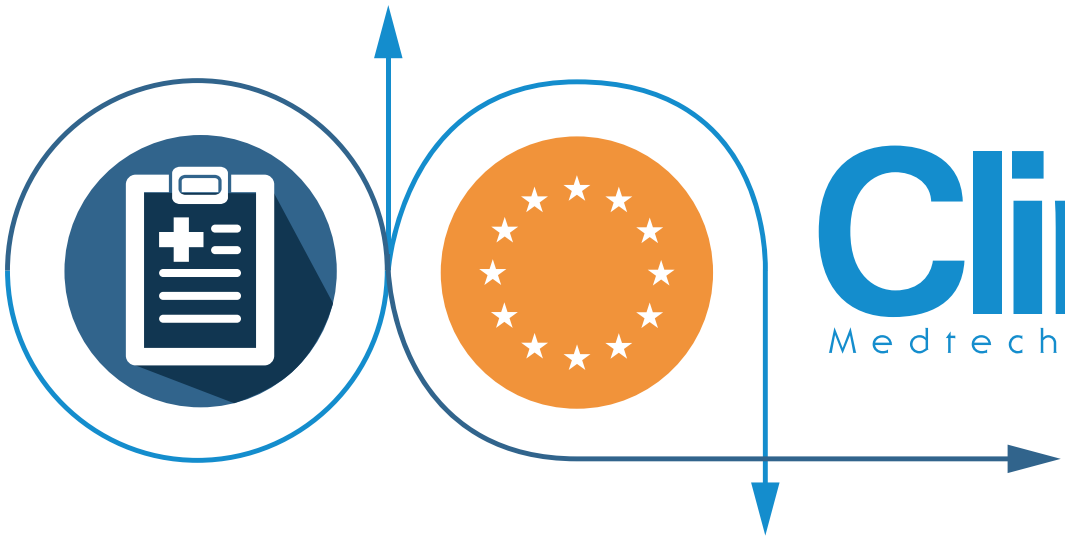

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# EU vs US Clinical Data Conundrum: Careful Assessment Needed With Current State Of Flux

By Amanda Maxwell, 10 November 2015

**WHERE ARE COMPANIES BEST ADVISED** to obtain their clinical data, the EU or the US, and why? These are questions Amanda Maxwell put to Patrick Biggins and Michelle McDonough of US consultancy Musculoskeletal Clinical Regulatory Advisers

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There are perennial questions over which market has the more stringent regulatory system – the US or the EU.

Historically, the consensus was that the US was the more stringent and it has been fiercely defensive of its position. Now the balance is altering as the regulatory systems undergo reform, especially in the EU, and companies need to examine more closely the best market for obtaining clinical data.

Patrick Biggins, vice-president, quality assurance and manufacturing, and Michelle McDonough, senior associate, regulatory and clinical affairs at US consultancy Musculoskeletal Clinical Regulatory Advisers, explained that the question has to be examined on a case-by-case basis, and explained what factors will influence the final decision in the current regulatory environment which is changing on both sides of the Atlantic.

They spoke to *Clinica* shortly after Jeff Shuren, director of the US FDA's device center, reopened the debate earlier this month on whether the EU or the US offers the best or most effective medtech regulatory system.

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There, he noted the "big question FDA is constantly tackling is whether the agency can sufficiently reduce the time and cost of bringing a product to the US market so that sponsors feel confident, but doing so without compromising that standard of reasonable assurance of safety and effectiveness". He acknowledged that if manufacturers do not have that confidence, new devices will not come to market in the US.

So what does MCRA think? Certainly, McDonough notes that FDA is highly critical of studies run outside the US. But the subject is a complex one and to assess which market is the optimum environment for device companies to obtain clinical data requires some in-depth research.

**Clinica:** *There has long been a perception that the US is much tougher in terms of clinical data requirements than the EU. Do*

*you think this continues to be the case? Or are there particular product types where it may not be – and if so, could you please give details?*

**Michelle McDonough:** There are two major differences between the US and EU clinical data requirements. The first is the requirement to demonstrate the performance of the device in the EU versus the effectiveness of the device in the US. Both markets require the sponsor to demonstrate safety, but the effectiveness requirement in the US typically requires the clinical data to reach a higher bar. If a device is effective, it can be determined that the device performs as intended.

The second is that clinical data is required for all devices in the EU; whereas in the US, clinical data is generally only required for devices that are Class III, or Class II devices that raise new questions of safety or effectiveness. While a prospective, clinical study is not required for all devices in the EU, a clinical evaluation report must be completed evaluating clinical data and/or published literature, as well as, vigilance data.

So while the clinical study requirements in the US are generally considered more stringent, the EU requirements could be considered more burdensome since every sponsor's device requires an extensive clinical evaluation report. Additionally, with the new proposed EU regulations, the preconceived gap between in EU and US data will most likely significantly decrease.

**Patrick Biggins:** The clinical data requirements in the EU for the musculoskeletal area, in which we specialize, are governed by the Medical Device Directive (MDD), 93/42/EEC, amended by 2007/47/EC. If clinical data is required by the notified body to obtain the CE Marking for a product, the manufacturer will need to be prepared to work with several entities to develop a clinical investigation notification, the precursor for a clinical study.

The entities will include the respective notified body, a research ethics committee, a physician or healthcare facility sponsor and a specific national healthcare regulatory agency such as the UK's Medicines and Healthcare products Regulatory Agency (MHRA).

The amount of information to provide to the healthcare regulatory agency usually differs from country to country; however, all of these agencies will require the manufacturer to comply with the MDD requirements for clinical data.

**Clinica:** *What are the particular challenges in the musculoskeletal area in the EU/US?*

**MM:** The main challenge in the musculoskeletal area in both the EU and US is study design. It is very important to establish a study design, ie, patient population, and success criteria that not only addresses the safety and efficacy of the device compared to the control, but also supports the proposed labelling claims.

**PB:** The European Commission's Directorate General for Health and Consumers has created several MEDDEV guidance documents for manufacturers and notified bodies. Several of the guidance documents are related to clinical investigations or clinical studies, including the study design. These should be used to understand what must be included in the study design to CE mark the device.

**Clinica:** *Is there a one-size fits approach to deciding where companies should conduct their clinical trials?*

**MM:** No, we believe the best approach is to design a successful study for each company's immediate needs. In addition to the requirements and regulations (current and proposed), we'd take into consideration the device technology and the company's resources, timelines and budget. Option 1 could be an initial European study that can support CE marking approval and then act as the pilot study data for IDE approval in the US. Option 2 could be a trial designed to ensure that the requirements for EU and US approval are considered in a single study design.

**Clinica:** *The European Commission's proposal for a new Medical Device Regulation specifically raises the game when it comes to clinical data requirements – especially in terms of sponsors needing to carry out trials rather than rely on data. If you analyze these new requirements, do you think they are justified? Do you think they should be even tougher? And how do you think this will impact the decision companies make about where to carry out their clinical trials?*

**MM:** I believe the new requirements, as related to clinical data requirements, are justified given the current organizational structure of the EU approval system. Post-market surveillance is an important component of a company's quality to ensure that the device is functioning as intended and the benefits continue to outweigh the risks.

To adequately assess the device's performance, the company should have a plan in place that documents the reported issues associated with their device - with higher risk devices requiring post-market studies (similar to the US). Safety reporting to the overseeing regulatory body is also justified to allow the body to review device groups as a whole (similar to the US's MAUDE Manufacturer and User Facility Database).

Often, companies will carry out a trial in the EU prior to the US because of expected lower costs and requirements; however, if a company does intend to market in the US, we recommend performing the study to the US regulations and expectations. This ensures the study will follow ICH GCP guidelines (and ISO 14155, Clinical investigation of medical devices, also recognized in the EU as EN ISO 14155).

Additionally, if the EU requires a post-market study, it is most likely that a similar study will be required by the US. The EU notified bodies review clinical studies to ensure the essential requirements and ICH GCP guidelines are met while demonstrating the device is safe and performs as intended.

The majority, if not all, of these criteria are met by performing an IDE-approved US study; however, the reverse is not always true.

FDA is highly critical of studies run outside the US. One of the newly proposed regulations in the EU will give the opportunity for manufacturers to consult with an expert panel to ensure that the clinical investigation will meet all EU requirements. If the proposed regulation is approved, it is yet to be determined if this process will be effective or practical.

One consideration that we support is ensuring that the patient population is representative of both US and EU patients.

**PB:** The ultimate goal for a successful clinical investigation, or clinical study, in the EU will be obtaining the CE marking by providing clinical data on the performance of the product.

Recent developments in the EU have placed additional scrutiny on medical devices already on the market without clinical data.

One of the EU's Medical Devices Directive requirements is the collection and analysis of post-production information. Does this include clinical data? Manufacturers need to address this issue, and to understand that post-production information may eventually need to include relevant clinical data or a plan to obtain relevant clinical data in a timely manner.

**Clinica:** *Is there anything else you would like to mention?*

**MM:** Clinical evaluations are a necessary component of a device company's technical file or design dossier, but they require an extensive amount of time and expertise in order to sufficiently address the regulations and analyze the data.

**PB:** The medical device industry has recently experienced a greater number of inquiries by notified bodies regarding the content of a manufacturer's technical file or design dossier.

One focal point of these inquiries has been the manufacturer's risk management process with an emphasis on data, particularly post-production information. If a manufacturer previously obtained CE marking for a legacy product without clinical data in the clinical evaluation report, the question that should be asked is what data is now being analysed indicating the performance of the product is still providing benefit? And is there the need for a post-market clinical follow-up?

Manufacturers need to provide the necessary information to first obtain the CE marking and follow this with a method of continually monitoring the performance of the product by analyzing data.

**More information of clinical evidence requirements in the EU was recently featured in Clinica's article on the future of clinical evidence requirements for CE marking.*

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