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NEWSLETTER

The State of Medical Device Clinical Research

FDA and Acceptance of Medical Device Clinical Data from Studies Conducted Outside the United States

Good News: FDA will start accepting OUS clinical data in support of IDEs, 510(k)s, de novos, and HDEs, and not only for PMAs.

Not so good news: Only studies meeting FDA's definition of "adequate" and "valid scientific evidence" will be allowed to support US submissions - this could possibly raise the bar for OUS studies.

Good News: FDA is allowing sponsors to use the Pre-Sub route to gain early feedback on study design from the Agency before OUS study initiation. If sponsors are planning to use OUS studies in support of US submissions, knowing FDA's standing on the study brings value and predictability.

Not so good news: By engaging the FDA before commencing OUS studies, sponsors will add minimum of 3-4 months at the front end of OUS clinical studies, possibly eliminating some of the current expeditiousness.

How to navigate the global clinical research landscape?

Hiring a CRO with vast FDA experience and OUS operations to discuss OUS studies with the Agency and then conduct these studies abroad will ensure that data collected in OUS studies meets FDA's expectation for valid scientific evidence.

Background

Globalization is affecting many areas of medical device development. The state of clinical research has changed, with rising cost and increased approval timelines. This reality has caused sponsors to look globally when they prepare their regulatory and clinical strategies. Consequently, clinical research is becoming global, featuring multi-national studies involving sites in Europe including Eastern Europe, India, China, Australia, and South America alongside with US centers. As outlined in Makower et. al. 2010 (*"FDA impact on medical technology innovation"*), most medical devices obtain OUS approval before they embark on a US approval. This is true for large and small companies, as evident from Table 1.

Table 1: Examples of European vs. US Access to Market

Device Name	CE Mark	US Approval/Clearance
XIENCE V Coronary DES	2006	2008
CoreValve (TAVR)	2007	2014
MitraClip (for DMR)	2008	2013
In.Pact Admiral	2009	2014
Subcutaneous Implantable Defibrillator (S-ICD®) System	2009	2012
UroLift implant for BPH	2010	2013
Symplicity RDN System	2010	not yet
Lutonix Peripheral DCB	2011	2014
Parachute Ventricular Partitioning Device	2012	not yet
Nanostim	2013	not yet
Direct Flow Medical Aortic Valve	2014	not yet

It has become the norm that sponsors conduct one or more clinical studies outside of the US to obtain OUS marketing access and to acquire data to support US IDE application, 510(k) notification or de novo authorization.

The main reasons to conduct OUS studies are: 1. they support OUS marketing submission and help market access; 2. they are faster, less bureaucratic; 3. OUS sites oftentimes have better enrollment rates; 4. study cost is sometimes also a consideration. But the single, most valuable reason is reducing company monthly burn rate.

Up to now, the only situation codified in the CFR for which OUS studies for medical devices were acceptable was in support of PMAs.

So what just changed?

On 22 April 2015 FDA issued a draft guidance on the acceptance of clinical data from studies conducted outside of the US. This draft guidance document is in line with one of CDRH's 2015 strategic priorities, to Strengthen the Clinical Trials Enterprise. FDASIA of 2012 added a new provision to FD&C codifying that FDA shall accept clinical data from OUS studies in support of various medical device submissions, unless such data are found inadequate.

Key Takeaways from the FDA DRAFT Guidance

- FDA recognizes that clinical research is global
- Key consideration in the Agency's decision to accept OUS data will be whether that data are "valid scientific evidence".
- However, there are challenges for accepting OUS clinical data:
  - Different clinical conditions - different standards of care may affect the disease condition, the analysis of benefit and the acceptance of risk; facilities and operator's skills may be different from the US
  - Different study population, including disease state, demographics of the affected population and cultural differences, all of which could have impact on final safety and effectiveness analysis
  - Differences in regulatory requirements - the FDA recognizes that other geographies may have different regulatory requirements applicable to medical device clinical studies; a classical, yet underestimated, example is that in EU, to obtain CE marking, devices must demonstrate SAFETY and PERFORMANCE; effectiveness is not included in the requirements for CE marking clinical studies; this of course has led to cases in the past, where clinical studies successfully demonstrated safety and performance in EU and devices obtained CE marking, but when studied in an IDE study failed to demonstrate SAFETY and EFFECTIVENESS.
    - Oftentimes, sham-controlled studies are considered "unethical" by European Ethics Committees, who believe that performing a procedure that is not expected to bring any benefit (such as a sham) is not the right thing for the patient; however, FDA has

argued in many cases, that the only way to find out if a proposed new treatment will bring meaningful clinical improvement, hence outweighing the potential risks, is a sham-controlled study.

- Best approach - if sponsor is planning an OUS study and is hoping to later use the data to support US submission - consult with FDA before commencing that study.
- FDA is implying that they are willing to use OUS data in lieu of any US data if that data was acquired with FDA's prior feedback or if the data were collected under GCP and / or more protective local clinical regulations.
- Through examples, FDA is also communicating that even in cases when OUS data are acquired without FDA's prior feedback, the Agency is willing to work with such sponsors to identify the least burdensome, most practical approach to approval.
  - Bridging studies, post-hoc analysis of data and adding small US studies to the final clinical packet are some of the approaches.
- FDA is planning to amend the CFR (part 807, 812 and 814) to add provisions of accepting OUS clinical data in support not only of PMAs (as it was till now), but also in support of other types of medical device submissions, such as IDEs, 510(k)s, de novos and HDEs.

About Us:

✓ Preferred Clinical Research is a CRO with vast experience with FDA submissions and studies and now with operations in Eastern Europe.

✓ Eastern European sites offer investigators with immediate capabilities to take on new studies, expedited regulatory approval and fast enrollment.

✓ We can support medical device studies in Bulgaria, the Baltics, Poland, and Rumania.

✓ Because of our experience with FDA, we have the knowledge to run global studies that meet FDA's expectations for being *"adequate under applicable standards"*.