This article discusses the early consultation process for medical devices in the EU and US and key considerations when planning such a meeting.

Developing a Global Strategy for Early Consultations

Are you developing an innovative medical device? Does it employ a novel technology? Does it provide novel diagnostic information or therapeutic benefit? Is it a combination or borderline product or a companion diagnostic? Do your plans to demonstrate safety, performance and/or efficacy utilize an approach that regulators have not seen before? Is your clinical evaluation based on equivalence? Or are you planning to conduct a clinical trial to support the device development effort? If the answer is yes to any of those questions, early interaction with regulatory bodies may reduce regulatory risk and reduce approval cycles. This article focuses on strategic pre-market regulatory considerations and touches on issues device manufacturers must consider in this situation.

The decision process to determine when to request consultation needs to take into account business goals and timing as well as technical considerations. Business goals frequently drive decisions that determine which regulatory agency is contacted first. However, earlier rather than later consultations with regulators may prevent a company, who may be somewhat unsure of the correct regulatory path to take, from making costly mistakes later on in the development lifecycle.

Prior to any engagement with a regulatory agency, device manufacturers should, at the very least, identify an intended use and classification for the device, and have a basic understanding of the applicable directives, essential requirements, guidance documents and precedents established for other similar devices. Device manufacturers also must evaluate their testing programs to identify areas where data expectations are generally harmonized, such as biocompatibility, and those where quite different data sets may be necessary. When deciding if a pre-submission meeting is appropriate, sponsors need to balance benefits of obtaining clarification from FDA in the pre-submission meeting against the time required to adequately prepare for a formal pre-submission meeting.
clarifications from FDA and other regulatory agencies against the time required to adequately prepare for the meeting. Furthermore, it is important to note the quality of feedback received from regulators is directly proportional to the quality and quantity of data provided prior to or during the consultation. However, too much information can hinder the efficacy of the consultation; the information provided and questions posed should be focused and easily assimilated to the desired goals of the interaction with the agency.

EU Specific Considerations

From a European perspective, you may engage with two regulatory stakeholders during the pre-market stage of the medical device development lifecycle: Competent Authorities and Notified Bodies. Figure 1 illustrates an idealized process identifying when pre-submission meetings occur and with whom. It should be noted there are other opportunities to engage with regulators at different stages in a medical device’s lifecycle not identified below.

**Figure 1: Idealized Process Map**

Medical device Competent Authorities, which may either be standalone agencies or reside within a Member State’s Ministry of Health, are responsible for the regulation of medical devices on the European market. A Member State’s Competent Authority is responsible for the review and approval of any clinical investigations conducted within their jurisdiction. There can be significant differences between each of the Member States, primarily in relation to processes and procedures.
It is important to determine:

- What is that application format: hard or soft copy or both, online or physical submission?
- What are the application fees?
- Are there pre-assigned application cut-off dates?
- What specific areas do you require feedback on, being strategic with your intent per geography?
- What documentation should be included in the application; what are the language requirements?
- What are the review and feedback timelines and how will this information be provided to you?
- Is Ethics Committee review and approval expected to be in place prior to submission or can parallel/sequential applications be made?
- Once approved, if an amendment is required, what is the process?

Such information can be gleaned through early engagement with the applicable Competent Authorities. However, Competent Authorities do not act as consultants; they will not be in a position to provide you with explicit advice relating to your product or study design, but rather more general guidance concerning expectations and best practices. Furthermore, as the European regulatory framework is based on a set of directives, individual Member States must transpose the requirements of these directives into their national laws. It is therefore important to determine if there are specific national requirements which are not explicitly covered by the directives. Consulting with a regulatory strategist with particular subject matter expertise and success in this area is highly recommended.

With respect to certification of medical devices in Europe or CE marking, this is conducted via a conformity assessment which ensures the device complies with the relevant essential requirements of the applicable medical device directive. These assessments are conducted by notified bodies of which there are more than 60 currently active, but not all may be suited to meet your needs. Notified bodies are designated based on their competency and may be restricted not only in terms of which of the medical device directives they operate under, but also in terms of what conformity assessment procedures they follow and for what range of product families. As such, identifying a shortlist of potential notified bodies which meet your high level requirements (i.e., directive, assessment route and product range) is a critical activity prior to any pre-submission engagements.

Similar to competent authorities, each of the notified bodies which make your shortlist will have their own unique processes and procedures. An initial inquiry to these notified bodies should be made to determine the business or administrative aspects of any applications, such as application process and forms, fees, scheduling, timelines, language requirements, etc. It also is important to reaffirm the designation information you based your search results on is still valid and the notified body can still offer the services which meet your needs. For example, in the case of combination products, additional discussion items would be required concerning the consultation process and the notified body's past experience with such products and their expectations for such product submissions.

While it may be possible to include some of the more technical or scientific aspects of your submission during your initial engagements with notified bodies, it may best be left to a more 'scientific' pre-submission meeting when the relevant expert assessor(s) are available. In advance of any scientific discussions, a summary
document and/or a slide deck which outlines the technical, clinical and biological characteristics of your product(s), including any questions you may have, should be made available to the notified body. This should ideally be made available at least one to two weeks in advance to allow for the expert assessors to fully appraise and prepare for the discussion. However, similar to competent authorities, notified bodies also are precluded from acting as consultants and can only offer general, non-specific regulatory advice.

It also is vitally important to clearly identify the device's intended use, classification and the rationale for this classification as well details as to how the clinical evaluation has been or will be conducted during discussions with either the notified body or competent authority. This last point is of particular importance given the increased scrutiny now being placed on the clinical evaluation process, in particular when such clinical evaluations are based on equivalency.

With respect to combination products, scientific opinion from a competent authority or the European Medicines Agency must be sought with respect to the quality and safety of the substance including the clinical benefit/risk profile of the incorporation of the substance into the device. It is highly recommended to engage with the agency conducting the scientific opinion consultation. For example, the European Medicines Agency strongly recommends a pre-submission meeting with the relevant notified body and device manufacturer preferably at least six months before the expected date of submission in order to assist them in preparing their application while the Health Products Regulatory Agency in Ireland recommends a pre-submission meeting two months in advance of a submission.

It also is important to note at this time the European regulatory environment is undergoing a period of transformation with two new regulations currently undergoing final legislative review and discussions between the European Parliament, European Commission and the Council of Europe. These new regulations, which may be agreed and finalized mid-2016 under the Dutch presidency of the Council of the EU, will replace the current directives. Manufacturers, together with their notified body, should now be considering how these proposed new regulations will impact them, whether the notified body will continue to support the current classification of products sold by the manufacture, and how the transition period will be managed by their notified body.

US Specific Considerations

Pre-submission meetings can be a useful tool to reduce regulatory risk, but are not required by FDA for medical devices. If a device developer is confident they fully understand FDA expectations for their medical device, it is acceptable not to request such a meeting. The US FDA has established a formal process for managing pre-submission meetings. The policy is described in the 2014 guidance document, "Meetings with Food and Drug Administration Staff." FDA does not charge a user fee for pre-submission meetings. If a meeting is appropriate, device developers need to prioritize several meeting parameters. First, as discussed at the beginning of this article, they need to identify the questions they wish to submit and determine if they have adequate data so FDA can draw clear conclusions. Next, device developers need to choose the type of meeting they wish to request. The table below summarizes various meeting types.

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<th>Table 1. Various Meeting Types</th>
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A study risk determination meeting is restricted to determining if the study poses significant risk (requiring an approved IDE), is a non-significant risk study, or if the study is exempted from the IDE regulation. If other questions need to be addressed, one of the other types of meetings would be more appropriate.

The pre-submission provides the greatest amount of flexibility and the broadest opportunity for obtaining feedback. The sponsor can discuss data expectations for any sections of the submission. Face-to-face meetings are generally limited to one hour so the number of questions also must be limited so they can be addressed in that time period. Questions should be supplemented with sufficient supportive information, including a suggested course of action and a rationale for those actions. Approximately two days prior to the meeting, FDA staff will provide an initial written response to the questions. The sponsor may then choose to delete questions, where the FDA response was adequate, from the meeting agenda. FDA staff also may include valuable additional information unrelated to the sponsor’s questions. The sponsor generally prepares meeting minutes after the meeting and sends them to FDA for review and, if they are accepted, they become the official meeting minutes.

Determination and agreement meetings are more formal than pre-submission meetings. FDA responses during these meetings are binding on the agency, as long as there are no significant changes to the device or new data related to safety or efficacy. In general, due to their more formal nature, these meetings usually provide fewer opportunities for information exchange than the pre-submission meeting.

**Key Points for a Successful Meeting**

The pre-submission meeting is an important opportunity to introduce your device and your development team to the regulators. It is important each sponsor participant clearly understand their role and carefully prepare their contributions to the meeting. The sponsor team should discuss their responses to likely questions from regulators. One sponsor representative should be the moderator and introduce each question, assure a concrete conclusion is reached, and track time to assure all the points are discussed. Immediately after the meeting, the sponsor team should prepare meeting minutes clearly state the conclusions reached and share...
Meeting, the sponsor team should prepare meeting minutes clearly state the conclusions reached and share the minutes with the regulators in order to confirm their understanding.

Conclusion

Early consultation with regulators can provide sponsors with a better understanding of data requirements and may help to reduce regulatory risk and improve approval timelines. However, including such interaction in the project plan often extends the project development timeline so the decision to request a meeting needs to be based on a consideration of both the risks and benefits of the agency interaction process. An effectively managed pre-submission consultation can reduce the marketing application review time and benefit the device developer, regulators and patients.

References


About the Authors

**Barry Sall** is a principal consultant at PAREXEL Consulting in Waltham, MA. He provides strategic regulatory support for developers of medical devices, in vitro diagnostics and combination products. He can be contacted at Barry.Sall@parexel.com.

**Dr. Paul Scannell** is a senior consultant at PAREXEL Consulting in Dublin, Ireland. He provides strategic European pre-market and post market regulatory advice to medical device manufacturers. He can be contacted at Paul.Scannell@parexel.com.

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RE: FDA Warning Letter (http://connect.raps.org/communities/all-discussions/discussions-moderation/message/?MID=9977)
Suggestion: go to OLRC Home (http://uscode.house.gov/)

RE: Test Method Validation for Devices (http://connect.raps.org/communities/all-discussions/discussions-moderation/message/?MID=9976)
Thanks to all of you for the responses. My client is doing some design work as a contractor for a medical device manufacturer. Some time ago, their customer received a warning letter for lack of te...

RE: FDA Warning Letter (http://connect.raps.org/communities/all-discussions/discussions-moderation/message/?MID=9975)
Redacted by FDA under FOIA B4 exemption from disclosure.

S...

RE: CRL Re-classification (http://connect.raps.org/communities/all-discussions/discussions-moderation/message/?MID=9973)
Thank for your time David!!

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SANDRA MOSQUERA

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Original Message:
Sent: 03-28...