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## SUCCESSFULLY INTERACTING WITH THE US FDA

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# **SUCCESSFULLY INTERACTING WITH THE US FDA**

**By Elisa D Harvey**

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This article will focus on how sponsors can improve and optimise their interactions with the US Food and Drug Administration (FDA) when trying to bring a new medical device into the US marketplace. Increasing the quality of a sponsor's interactions with the FDA can greatly improve the chances for a device to successfully navigate the FDA regulatory maze.

Getting a new medical device onto the US marketplace involves a complex series of steps, not least of which is convincing the FDA that you as the sponsor have met the regulatory standard for that type of device. Ten years ago the usual path for finding out whether the FDA agreed with a sponsor that the device should be allowed to be marketed in the US was to simply submit a marketing application for the device and wait the requisite 90 or 180 days for the official response. In 2007, this approach should be considered folly at best, and expensive and ill-advised at worst, for all but the very simplest of medical devices.

***Communication with the FDA at an early stage in the regulatory process is highly advisable***

Nowadays, for the most successful companies, interacting with the FDA occurs at a much earlier stage, and the nature of these interactions will, to a large extent, shape how successful a sponsor is at their ultimate goal - marketing approval or clearance for their device.

These interactions fall under the broad umbrella of what is known as the pre-IDE (Investigational Device Exemption) programme. In 1996, it was originally created to describe the informal interactions that could take place before a sponsor officially submitted an IDE application to gain permission to conduct a clinical study of their investigational device in the US, in order to better understand the FDA's expectations for the eventual IDE. The name pre-IDE has evolved to become a term of art since its inception, and now serves as the mechanism for interacting with the FDA for several other purposes, which will be described below. Now, the pre-IDE meeting has become the heart of the sponsor's interaction with the FDA.

But first, critical to having successful interactions with the FDA is having a clear understanding of its organisation, the FDA resources available to sponsors, and its regulatory mandate.

## **Organisation and Contact Information**

***It is important to understand the organisational structure of the FDA***

The FDA is a multi-layered organisation, and knowing who to contact and where they fit in the organisation can make a great deal of difference. Device sponsors will primarily be working with the Center for Devices and Radiological Health (CDRH), and even more specifically, the Office of Device Evaluation (ODE) or the Office of *In Vitro* Diagnostic Devices (OIVD) within CDRH. The ODE is divided

into five divisions:

- Division of Cardiovascular Devices (DCD);
- Division of General, Restorative and Neurological Devices (DGRND);
- Division of Reproductive, Abdominal and Radiological Devices (DRARD);
- Division of Ophthalmic and Ear, Nose and Throat Devices (DOED);
- Division of Dental, Anesthesiology, General Hospital and Infection Control Devices (DAGID).

***ODE comprises five divisions...***

The OIVD is divided into three divisions:

- Division of Chemistry and Toxicology Devices;
- Division of Immunology and Hematology Devices;
- Division of Microbiology Devices.

***...whereas the OIVD contains three divisions***

Each of the ODE divisions is further divided into three to five branches according to the area of the medical device. The organisation of the ODE and the OIVD, along with the current management and the telephone numbers for the divisions and branches, can be seen on the FDA website at [www.fda.gov/cdrh/organiz.html#ODE](http://www.fda.gov/cdrh/organiz.html#ODE). Email addresses and other contact information for any individual within the FDA can be found at the Department of Health and Human Services (DHHS) Employee Directory website (<http://directory.psc.gov/employee.htm>). Armed with this information, sponsors can determine who they need to contact with respect to their specific device questions.

## **FDA Resources**

Importantly, one of the first things any sponsor should do before contacting any member of the FDA staff is to check the FDA website ([www.fda.gov](http://www.fda.gov)). There is a vast array of useful information within this website including, but not limited to, information on the law (the *Federal Food, Drug and Cosmetic Act* (FFD&C Act) that is the basis for medical device regulation), the Code of Federal Regulations (CFR), the requirements for every submission type and device area, publicly-available databases, combination products, available guidance, and resources for small businesses, international businesses and consumers. Many questions can be answered by searching the FDA website, or at least refined, so that when sponsors do speak with FDA staff, they have already educated themselves to the extent possible.

***Sponsors should always familiarise themselves with the information on the FDA website before contacting a member of FDA staff***

## **CDRH's Regulatory Mandate**

Medical devices have been explicitly regulated since the 1976 Medical Device Amendments to the FFD&C Act. The mandate of CDRH is to establish reasonable assurance of the safety and effectiveness of medical devices and of the safety of radiological products marketed in the USA. To that end, the CDRH and ODE in particular have developed a comprehensive paradigm of regulations,

guidance documents and policies to inform sponsors of how to best accomplish this goal for their own medical device, in order to allow it into the US marketplace.

***Sponsors need to fully understand the relevant law, regulations, guidance and policies***

Any sponsor wishing to introduce a medical device into the US marketplace should first clearly understand the basis for the applicable law, regulations, guidance and policies regarding medical device oversight, and then use this knowledge to the fullest extent possible. This will maximise the chances of success when interacting with the CDRH.

## **Pre-IDE Programme**

Meetings with industry have become integral to the CDRH mission. The ODE and OIVD are committed to communicating and interacting with stakeholders and they now have well over 500 meetings per year with sponsors. The 1997 *Food and Drug Administration Modernization Act* (FDAMA) even explicitly required early collaboration with the regulated industry in determining data requirements for clinical studies. Pre-IDE meetings were originally conceived as an informal mechanism to improve the quality of IDE applications from sponsors, by providing feedback before an official submission was made. While it has definitely provided a clear path for sponsors to receive feedback for their proposed bench and/or animal testing plan as well as the proposed clinical test plan and statistical methods for their eventual IDEs, it has also become an invaluable mechanism for feedback in several other areas as well, most notably for:

***Pre-IDE programme is particularly helpful for obtaining advice on...***

- non-significant risk, exempt or post-market studies which do not require IDEs but which will generate data to support an eventual marketing submission; *and*
- studies conducted outside the USA which do not require an IDE but which will generate data to support an eventual marketing submission.

### **When to Have a Pre-IDE Meeting**

There is a right and a wrong time to have a pre-IDE meeting with the FDA. To be most productive for the sponsor and the FDA, there must be a minimum amount of information available. Therefore, prior to proof of concept, or before specific questions can be formulated for the FDA, a pre-IDE meeting is not encouraged. Rather, telephone or email interactions are usually considered sufficient. A face-to-face pre-IDE meeting is encouraged for two later phases:

***Face-to-face pre-IDE meetings should not be considered until...***

- the preclinical phase, where the prototype has been evaluated in preliminary animal models, and there is a proposed clinical application; *and*
- prior to expanding clinical trials from feasibility to the pivotal trial phase (i.e. feasibility studies have been completed, device design has been finalised, animal studies are completed, and the proposed pivotal trial protocol has been drafted).

## Logistics

There is a definite timeline to planning and scheduling a pre-IDE meeting and the background package that must be submitted in advance of the meeting. First, a complete package must be received by the FDA before a meeting will be scheduled. When a package is received, the CDRH logs in the document as a pre-IDE, assigning it a document reference number, starting with 'I', followed by the year it was received (e.g. '07'), followed by the consecutive number of that pre-IDE for the year (e.g. '0034' for the 34th pre-IDE received by the CDRH in 2007). There is, as yet, no fee for pre-IDE submissions, making them even more attractive to sponsors.

***No fees are currently charged***

The pre-IDE submission is then assigned to the reviewing division, which logs it into the division tracking system and sends an acknowledgement letter to the submitter. The branch chief assigns the document to a lead reviewer who also determines the need for consulting reviewers. Pre-IDEs have a non-statutory review timeframe of 60 days; that is, CDRH does not have a 'hard' review deadline imposed by the law, but they have committed to completing pre-IDE reviews in a reasonable timeframe to the best of their ability, and this has been set at 60 days. The review timeframe allows the FDA review team time to receive their copy of the pre-IDE, review it, have an internal meeting with the review team to go over the questions posed by the sponsor, prepare memos, and schedule a meeting with the sponsor. Therefore, expect a meeting to occur no sooner than about six to eight weeks after the FDA has received the document.

***Reviews are usually concluded within 60 days...***

***...and a meeting is typically scheduled six to eight weeks after FDA receives the document***

Individual review divisions may have their own checklists or procedures for handling pre-IDEs; it is important to check with the division before submitting to optimise your own document to meet their needs. In addition, if substantial additional information is provided after the initial package is received and a meeting is scheduled, the FDA may well postpone or cancel the meeting.

Typically the FDA will allow for a one hour meeting maximum; in some cases they may allow for a longer meeting for exceedingly complex technologies or issues. The branch or division will clarify whether more than one hour can be allotted to a meeting. At the time of the meeting, the FDA will provide an attendance sheet with names and affiliations of all present, which will be provided to the sponsor. In addition, they will typically ask for a copy of any PowerPoint® presentation, and will generally expect the sponsor to take minutes of the meeting to be shared and reviewed by the FDA, and then finalised by the sponsor. These minutes will be added to the pre-IDE file as part of the record. Follow-up information shared afterwards can also be added to the pre-IDE file as a pre-IDE supplement.

***Pre-IDE process should not be considered a tool for negotiation***

It is important to remember what the pre-IDE meeting is intended to be, and what it is not intended to be. It is an informal, but invaluable, way to obtain Agency feedback on a proposed test plan. However, sponsors should not consider the pre-IDE mechanism to be a tool for negotiation. Also, they should not expect to be able

to use the Agency as their own regulatory consultant. Nor is it an iterative process, with unlimited opportunities to go back to the Agency before submitting an application. The CDRH has too many sponsors to meet with nowadays to be able to meet with each one on multiple occasions. The initial pre-IDE meeting (and perhaps one follow-up) is the one where you need to glean your information. It is also not intended to be a modular review of sections of an eventual application. Perhaps most importantly, the pre-IDE process should not be used as a means to get a 'pre-review' of data before it is officially submitted to the Agency. In these days of limited resources and user fees for review of marketing applications, it is likely that the CDRH will refuse to review such a package of information. Rather, the process should be used to review proposed protocols for bench, animal and clinical testing. As it is an informal process, it also cannot be expected to be as in-depth as the review of an IDE or marketing application. It is best used to answer a few specific, focused questions about a sponsor's planned approach. Finally, because the pre-IDE process is informal, none of the feedback that is obtained during the pre-IDE process should be considered legally binding on either the Agency or the sponsor, nor can it be used as a method for resolution of a dispute between a sponsor and the Agency.

***A meeting is best used to answer a few specific questions about a sponsor's planned approach***

#### **Content of a Pre-IDE**

To make the process most effective, the content of a pre-IDE package should be carefully considered. There is no absolute required content or format, although there are suggestions from the Agency at the following website: [www.fda.gov/cdrh/devadvice/ide/approval.shtml#pre\\_ide](http://www.fda.gov/cdrh/devadvice/ide/approval.shtml#pre_ide). The basic elements which should be a part of any pre-IDE package are the following:

***A pre-IDE package should typically contain...***

- a covering letter clearly identifying the submission as a pre-IDE;
- a proposed agenda for a meeting, including a specific allotment of time for each proposed agenda item;
- a list of the proposed participants on behalf of the sponsor as well as a suggestion for the skills and expertise required for FDA attendees;
- a list of several specific and focused questions to the Agency for which the sponsor would like feedback by the end of the meeting;
- some proposed dates or ranges of dates that would be appropriate for meeting with the Agency;
- the background information needed on the device and the proposed protocols (in sufficient detail) that the FDA will need in order to provide the feedback the sponsor is requesting.

Sponsors frequently ask how long a pre-IDE submission should be. A general rule of thumb is to make the package long enough to enable the FDA reviewers to be able to sufficiently understand the device, its principle of operation, and what is known about its performance thus far in order to provide specific feedback in the areas of interest. It should go without saying that the package

should be organised, concise and easy to follow. Anything that makes the FDA reviewer's job easier will ultimately benefit the sponsor. Packages probably should not be as short as five pages, or as long as a 1000 pages. Instead, most packages fall in the range of 50 to 100 pages. Obviously for complex technologies such as combination products, packages may need to be longer to provide the requisite information. Any question as to content and length can be posed to the reviewing branch and division for their particular needs.

***Submission packages are usually 50 to 100 pages in length***

### **Formal Pre-IDE meetings**

In addition to the informal pre-IDE meetings, FDAMA legislation also mandated that the CDRH should make available 'early collaboration' meetings to the regulated industry, and these meetings are formal and binding on both the FDA and the sponsor. These types of meetings can be considered when a sponsor desires more binding and official feedback for a particular device and its indication. The CDRH has provided a guidance document describing the purposes of these meetings and how to go about obtaining a determination or agreement meeting. According to the guidance ([www.fda.gov/cdrh/ode/guidance/310.html](http://www.fda.gov/cdrh/ode/guidance/310.html)), a Determination Meeting is available to anyone anticipating submitting a pre-market approval application and is intended to provide the applicant with the Agency's determination of the type of valid scientific evidence that will be necessary to demonstrate that the device is effective for its intended use. As a result of this meeting, the FDA will determine whether clinical studies are needed to establish effectiveness and, in consultation with the applicant, determine the least burdensome way of evaluating device effectiveness that has a reasonable likelihood of success. The applicant can expect the FDA to determine if concurrent randomised controls, concurrent non-randomised controls, historical controls, or other types of evidence will be acceptable. The FDA's determination is written, shared with the applicant within 30 days following the meeting, and is binding upon the Agency, unless it would be contrary to public health.

***Two types of formal, legally-binding, pre-IDE meetings can take place between a sponsor and the FDA***

The other opportunity for a meeting established by FDAMA is an Agreement Meeting, which is open to any person planning to investigate the safety or effectiveness of a Class III product or any implant. Thus, unlike the Determination Meeting, the Agreement Meeting is available to submitters of pre-market notifications (510(k)s) for eligible devices. The purpose of this meeting is to reach agreement on the key parameters of the investigational plan, including the clinical protocol. The meeting is to be held within 30 days of the receipt of a request for such a meeting. Any agreement reached in this meeting is also written, shared with the applicant, and made part of the administrative record. It is binding on the Agency and may be changed only with the written agreement of the applicant or when there is a substantial scientific issue essential to determining the safety or effectiveness of the device.

***Agreement Meetings may be used by a sponsor planning to investigate a Class III device or implant***

Both Agreement and Determination Meetings require a

background package to be submitted, and this submission is logged in to the CDRH as a pre-IDE submission but is coded for these specific meeting types.

### **Why a Face-to-Face Meeting?**

The pre-IDE process was created to provide a flexible and informal way to create a dialogue between sponsors and the FDA at an earlier stage in device development than existed previously. As such, a sponsor can use it to get feedback in a variety of ways - through a letter (though still informal and non-binding), a facsimile, an email, a teleconference or a face-to-face meeting. While not every question a sponsor may have would require a face-to-face meeting with FDA representatives, these meetings have significant value beside the actual information exchange. Getting to know a review team, establishing a rapport and collaborative working relationship will stand any sponsor in good stead for the duration of that project and others to follow. Although there is an upfront cost in time, effort and resources to both the FDA and sponsors for using this approach, the potential benefits - optimally designed testing and development plans that will expedite review and approval, minimising surprises to both sides, a more collaborative approach, and ideally savings in both time and money - may ultimately far outweigh the initial cost.

*Face-to-face meetings offer a number of benefits apart from the actual information exchange*

### **Top Ten Tips for Successfully Interacting with the CDRH**

1. Do your homework. Read the available guidance documents, information and requirements available on the FDA's website. Nothing bothers a reviewer more than questions from a sponsor that could easily be answered by simply checking the website.
2. Submit a clean, well-organised document. Proof-read, paginate consecutively and then have an uninvolved colleague or consultant proof-read it again before submitting it to the FDA.
3. Know what you want to ask the Agency. A sponsor who is not sufficiently focused will not get focused feedback.
4. Take the feedback that the FDA offers you seriously. Even if you disagree with the feedback you receive, you should nevertheless understand the Agency's reasoning for their position so that you can provide the strongest argument for your position.
5. Do not have a meeting until you are ready, and when you do have a meeting, prepare carefully. Have a dress rehearsal of the planned presentation. Check with the reviewing branch or division to be sure you are providing what they need.
6. Allot no more than 25% of the meeting time to the background information presentation. One of the biggest mistakes made by sponsors is to spend an inordinate amount of time talking at the meeting, leaving insufficient time to listen to and receive the FDA's feedback. Make the most of that meeting opportunity and manage the time carefully.

*Feedback obtained from the FDA will have a greater value if the questions are focused*



7. Do not have too many people attending on behalf of the sponsor - the more individuals involved in a meeting, the less productive it becomes. Have the right people in attendance, especially decision-makers for the sponsor who can speak with authority at the meeting.
8. Do not add new information or change existing information just before a meeting. Even if the meeting is not postponed or cancelled, it will severely decrease the usefulness of the meeting by introducing information that the FDA has not had a chance to review, making them unlikely to provide any feedback at the time of the meeting.
9. If you as a sponsor, especially as a small or start-up company, do not have adequate expertise and experience in FDA and CDRH regulatory affairs, then obtain the services of a reputable consultant with experience in the specific device area of interest. Engineering and marketing experience are no substitute for understanding the regulatory requirements and pathway involved for a device.
10. When in doubt about any aspect of the pre-IDE process and how it applies to your device and project, ASK the reviewer, branch or division.

***Fewer attendees make for a more productive meeting***

## Summary

The pre-IDE process has become a critical part of device development since its inception over 10 years ago. Although it is an optional exercise, the value it provides to sponsors in terms of decreasing uncertainty, establishing working relationships with FDA staff, and clarifying expectations makes it one of the most important interactions a sponsor can have with the CDRH. Properly preparing for and using the pre-IDE process to a sponsor's best advantage therefore becomes essential for success of the device development plan. The FDA is very willing to provide their feedback at this earlier stage in order to improve the quality of submissions, and ultimately the quality of new devices entering the US marketplace - it is an opportunity that should be considered an essential step in the development of any device intended for the US market.

***Early interaction with the FDA should be an essential step in the development of a device for the US market***

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