Companion diagnostics and the FDA pre-submission programme

At first glance, the new pre-submission programme looks far more complicated than the current pre-IDE process. And in some cases it appears that there are redundancies between the pre-submission applications (IDE and IVD, for example). However, on closer review, this new process – if used properly – will allow sponsors to have a more focused discussion with the FDA throughout the product development process. For example, if a sponsor is planning to submit a 510(k) application for a device with a well-established predicate device and clear roadmap for demonstrating substantial equivalence, then a 510(k) pre-submission application will allow the sponsor to ask very focused questions on that device, without having to go into a lot of detail about the device and clinical study plans.

But the question remains, how does a sponsor go about applying the new pre-submission process to a companion diagnostic device? While it is true that the guidance is still draft and could thus undergo some revisions in the future, there is a way for companies to use the new process today to obtain specific advice from the FDA at key points in the development process.

Pre-submission roadmap for companion diagnostics (CoDx)
As Table 1 indicates, the pre-submission process can be tailored to meet the specific goals of a companion diagnostic submission. Within the types of applications listed, there are three that are most applicable (and useful) to companion diagnostic co-development: IVD, IDE and premarket approval (PMA).

It is worth discussing PMA first. Although the FDA allows for the possibility of a 510(k) application for a CoDx device, our experience thus far has been that these devices are Class III because of their use in selecting or monitoring patients for the associated therapeutic. So for the sake of this article, we will focus on the PMA pre-submission.

Since many CoDx devices will be used as part of a Phase III clinical trial, it is also safe to assume that there will need to be an IDE submission as part of the regulatory pathway. Therefore it makes sense to include an IDE pre-submission application in the regulatory plan.

However, before companies even begin the development process, they should have an initial discussion with the FDA on the proposed device (particularly software and instrumentation), the clinical and nonclinical study plans, and of course the proposed “intended use” and “indications for use” statements. This is what many sponsors previously did through the pre-IDE application, but now it makes sense to incorporate this into the IVD pre-submission application.

One way to look at how these various submissions and meetings would fit into the overall development timelines for the CoDx device and the therapeutic is represented in Figure 1.

As shown in Figure 1, once a company has gathered enough preliminary data to demonstrate the feasibility of using the biomarker as a companion diagnostic, and once it has a working prototype assay, it can begin to assemble this information into an IVD pre-submission document. In addition to a description of the device, the sponsor will want to propose an “intended use/indications for use” statement and outline the clinical and nonclinical studies that would be required for the CoDx device. As with the previous pre-IDE process, the key first step in assembling this application is to start with the key questions the company would like the FDA to review. For example:

Overview of the pre-submission process
The FDA has outlined in the new pre-submission programme six different submission categories. These are presented in Table 1, along with some general comments on the purpose of each meeting.
should be filed no less than 90 days prior to the PMA submission, (PMA) pre-submission, is the most straightforward. This application approval on the IDE.

The minimum amount of information required to get a provisional clinical testing, as well as get feedback from the agency on what is anticipated changes to the device that may occur during pre-submission application is also a good place to get feedback drug will dovetail into the IVD clinical validation studies. The IDE submission and how the proposed clinical studies for the CoDx device. Possible questions for the FDA in this document would be:

- Does the FDA agree with the regulatory pathway for the CoDx device?
- Are there comments or concerns that the FDA has with the intended use/indications for use?
- Does the FDA have any comments or advice on the clinical study plans, particularly the data analysis plan?
- Does the FDA have any comments on the proposed software for the CoDx device?
- Is the proposed method comparison study appropriate?
- Does the FDA have any comments on the proposed bridging study (if applicable)?

The IVD pre-submission application should be filed as early in the product development process as possible so that the advice from the FDA can be incorporated into the design and development plan for the CoDx device. The longer this submission is delayed, the less useful this information will be to the drug and IVD partners.

Once performance of the CoDx device has at least been characterised (if not verified), the pharmaceutical and IVD sponsors should file an IDE pre-submission application with the FDA. As shown in Figure 1, the focus of this application is going to be on the clinical trial design and other key elements of a future IDE submission for the CoDx device. Possible questions for the FDA in this document would be:

- Are the nonclinical study protocols sufficient to determine the safety of the CoDx device prior to initiation of the Phase III clinical study?
- Are the primary and secondary endpoints appropriate?
- Is the statistical analysis plan and sample size appropriate for the proposed clinical study?
- Is the plan for collection, storage and testing of the clinical samples from the drug trial acceptable?

Here the sponsors really need to focus on the key elements of the IDE submission and how the proposed clinical studies for the drug will dovetail into the IVD clinical validation studies. The IDE pre-submission application is also a good place to get feedback on any anticipated changes to the device that may occur during clinical testing, as well as get feedback from the agency on what is the minimum amount of information required to get a provisional approval on the IDE.

The final pre-submission application, the postmarket approval (PMA) pre-submission, is the most straightforward. This application should be filed no less than 90 days prior to the PMA submission, and should be used to get feedback from the FDA on the format and acceptable timing of the PMA submissions, particularly for a modular submission. Questions for this pre-submission application could include:

- Is the proposed data format acceptable to the FDA?
- Is a modular PMA acceptable? If so, does the FDA have any preference in the contents and timing of the modules?
- Does the FDA have any concerns about the plan to address protocol deviations?
- What (if any) post-approval studies should be contained in the PMA?

Again, as with the IVD pre-submission, it is important to file the PMA pre-submission at the appropriate time. In fact, in its draft guidance document, the FDA asks sponsors to file PMA pre-submission applications at least 90 days prior to the PMA submission to allow time for agency comments to be incorporated in the final application.

### Table 1: Types of FDA pre-submission applications.

<table>
<thead>
<tr>
<th>Pre-submission application</th>
<th>Purpose</th>
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<tbody>
<tr>
<td>IDE</td>
<td>Obtain feedback from the FDA on the various elements of a future IDE submission. This pre-submission can also be used to obtain advice on any contemplated changes to the device after the IDE has been submitted.</td>
</tr>
<tr>
<td>NSR, Exempt, OUS</td>
<td>To obtain advice from the FDA on proposed studies for non-significant risk (NSR), exempt, or outside-the-US (OUS) devices.</td>
</tr>
<tr>
<td>510(k)</td>
<td>To obtain advice from the FDA on the proposed predicate device and any planned studies intended to demonstrate substantial equivalence.</td>
</tr>
<tr>
<td>PMA</td>
<td>To discuss with the FDA any important issues or considerations related to formatting, filing, electronic data, etc, for a future (90 days or greater) premarket approval (PMA) submission.</td>
</tr>
<tr>
<td>IVD</td>
<td>To obtain feedback on the intended use/indications for use, validation study designs, software, etc. specifically related to in vitro diagnostic devices.</td>
</tr>
<tr>
<td>HDE</td>
<td>To obtain feedback from the FDA on the clinical and nonclinical elements of a future (90 days or greater) humanitarian device exemption (HDE) application.</td>
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### The filing, review and meeting process

As with pre-IDE applications, the FDA requires an original and two copies for each application. It also requires that all pre-submission applications contain the same general information, which is listed in the draft guidance document. Much of this information is similar to past pre-IDE submissions: device description, intended use, discussion of feedback mechanism (meeting, teleconference, written comments only), table of contents, cover letter, and a discussion of any previous submissions.

However, the FDA is now asking that each application also has an overview of the product development process, including a discussion of any completed nonclinical or clinical studies. This status update should help developers and their pharmaceutical partners obtain important real-time feedback on the project and any concerns the FDA may have with the studies conducted to date.

Because the FDA is looking for specific content in each of the pre-submission applications, they will be reviewing each application for completeness, and will only schedule a meeting if all the elements are present and acceptable. Once the meeting has been scheduled, the review process is similar to the previous pre-IDE process, with the FDA sending written comments to the sponsor at least three days prior to the meeting.

Similarly, a meeting can be held either face-to-face at the FDA or via a teleconference call. Sponsors are asked to draft the minutes

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of the meeting, which will then be sent to the FDA for review. Final minutes will be issued by the FDA within 30 days of the meeting. Any issues resulting from a pre-submission meeting should be addressed in either a future pre-submission application or in a regulatory filing (IDE, PMA, etc) as appropriate.

The role of alliance management in the pre-submission process
It is important to apply some basic alliance management principles to the pre-submission process. One of the benefits of going through the pre-submission process is that both the FDA and the sponsors can crystallise the goals and deliverables for the CoDx development project. In order to do this successfully, there are some alliance management practices that any regulatory team member can apply to improve the process and make the day-to-day partner (and FDA) interactions more effective. Key concepts and activities include:

- **Partners should understand each other’s business.** The recent increase in CoDx partnerships has highlighted how little either side knows about their partner’s business. This is especially true for the drug partner. Companies should not assume they understand what assay development and validation is simply because they have some past experience with it in drug development. Developing a diagnostic assay is very different from developing a drug assay.

  The same holds true for the two main pathways to market – distributed kits and laboratory-developed tests (LDTs). Each has its own unique set of strengths and weaknesses (particularly in the regulatory function), and understanding what those are and how best to manage them is key to having a successful CoDx development project.

- **Establish good communications channels.** Transparency is the key to any successful alliance. While there are certain aspects that cannot be shared with a partner, the regulatory teams should (for the most part) be able to talk freely. Having frequent dialogues with their regulatory counterparts will help to understand the issues they are facing and also offer the opportunity to learn more about how to take a diagnostic (or drug) through the regulatory process. The FDA’s Center for Drug Evaluation and Research (CDER) and Center for Devices and Radiological Health (CDRH) are very different organisations, and the more regulatory team members can learn about how each works, the better equipped they will be to understand the regulatory risks involved.

  - **Pre-submissions are for the diagnostic.** When putting together a pre-submission for a diagnostic, it is unnecessary to go into great detail about the drug (or its therapeutic effectiveness) in the submission. While it is important that the CDRH understands the drug and how the CoDx device will support it, the submission should stay focused on the basic information that the CDRH will need in order to understand how the device is intended to be used with the drug.

  - **Ask the right questions.** The most important use of a pre-submission is to ask the CDRH the key questions necessary to create a successful regulatory filing. Companies should use the pre-submission programme to get clarity on questions around issues like bridging studies, the use of banked samples, and whether fully validated assays are needed prior to starting Phase III testing. Both the drug and device regulatory teams need to spend a lot of time drafting and honing these questions, so that each partner gets the feedback they need from the FDA to take the next step in the process.

**Conclusion and final thoughts**
Though the previous pre-IDE process was a useful tool for IVD developers, it was somewhat nebulous and required some skill and experience on the part of the sponsor to obtain meaningful advice from the FDA. Further, the lack of a defined process made it difficult for new IVD manufacturers and pharmaceutical partners to understand what was required from them to provide a relevant submission for the FDA to review.

With the draft guidance on the pre-submission programme, the FDA is attempting to clearly define the pre-submission process and the requirements for each type of application. The result should be increased communication between the FDA, sponsors and the pharmaceutical stakeholders, which ultimately should result in a more efficient regulatory submission review and approval process. Further, by following a regulatory roadmap using the pre-submission programme, there should be greater transparency in the companion diagnostic development process, making it easier for drug developers to understand the status of the project and the risks associated with the device approval.