Draft Guidance for Industry and FDA Staff

Medical Devices: The Pre-Submission Program and Meetings with FDA Staff

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.
Document issued on: July 13, 2012

You should submit comments and suggestions regarding this draft document within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852. Alternatively, electronic comments may be submitted to http://www.regulations.gov. Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this document, contact the CDRH Program Operations Staff (POS) at 301-796-6560 or CBER's Office of Communication, Outreach and Development at 1-800-835-4709 or 301-827-1800.

When final, this document will supersede Pre-IDE Program: Issues and Answers - Blue Book Memo D99-1, dated March 25, 1999.

U.S. Department of Health and Human Services
Food and Drug Administration

Center for Devices and Radiological Health

Center for Biologics Evaluation and Research

Preface

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Additional copies are available from the Center for Devices and Radiological Health (CDRH) through the Internet. You may also send an e-mail request to dsmica@fda.hhs.gov to receive an electronic copy of the guidance document or send a fax request to 301-847-8149 to receive a hard copy. Please use the document number (**1677**) to identify the guidance document you are requesting.

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Evaluation and Research (CBER) by written request, Office of Communication, Outreach and Development (HFM-40), 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, by telephone, 1-800-835-4709 or 301-827-1800, by email, ocod@fda.hhs.gov, or from the Internet at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/default.htm.

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Draft Guidance for Industry and FDA Staff

Medical Devices: The Pre-Submission Program and Meetings with FDA Staff

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance document. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance document.

I. Introduction

Since its establishment in 1995, the pre-Investigational Device Exemption (pre-IDE) program has been a successful resource for both medical device applicants[1] and the Food and Drug Administration (FDA). Originally, this program was designed to provide applicants a mechanism to obtain FDA feedback on future Investigational Device Exemption (IDE) applications prior to their submission. Over time, the pre-IDE program evolved to include feedback on other device submission program areas, such as Premarket Approval (PMA) applications, Humanitarian Device Exemption (HDE) applications, and Premarket Notification (510(k)) Submissions, as well as to address questions related to whether a clinical study requires submission of an IDE. The purpose of this guidance is to update the pre-IDE program to reflect this broader scope and make important modifications to reflect changes in the premarket program areas as a result of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law 110-85).[2] This guidance also broadens the scope of the program to include those devices regulated by the Center for Biologics Evaluation and Research (CBER).[3] Accordingly, the name for this program is being changed from the pre-IDE program to the Pre-Submission (Pre-Sub) program.[4]

[1] For the purposes of this guidance document, manufacturers or other parties who submit an IDE or marketing application to the Agency are referred to as applicants or sponsors.

[2] The Medical Device User Fee Act of 2007 is scheduled for reauthorization this year by Congress. This guidance will be revisited and modified as appropriate based on any legislation that might affect the presubmission program.

[3] This guidance does not address meetings to discuss medical devices that are regulated as biologics under the PHS Act by CBER. To request a meeting in advance of submission of an IND or BLA to CBER, see CBER SOPP 8101.1: Scheduling and Conduct of Regulatory Review Meetings with Sponsors and Applicants; available at

The main purpose of the Pre-Sub program remains the same as the pre-IDE program: to provide the opportunity for an applicant to obtain FDA feedback prior to intended submission of an IDE or marketing application. The Pre-Sub program can also provide a mechanism for the Agency to provide advice to applicants who are developing protocols for clinical studies for which an IDE would not be required, such as studies of non-significant risk (NSR)[5] devices or for clinical studies conducted outside of the U.S. to support future U.S. marketing applications. Consequently, the Pre-Sub program can provide an efficient path from device concept to market while facilitating the agency's goal of fostering the development of new medical devices.

FDA provides advice to industry during the developmental stage of future 510(k), IDE, PMA, and HDE submissions in a number of ways. The Pre-Sub program is one mechanism that FDA uses to guide and answer industry questions; however, there are other mechanisms, such as the CDRH Device Advice website,[6] CBER's Manufacturers Assistance and Technical Training Branch,[7] and relevant guidance documents. These mechanisms, as well as 510(k) summaries or summaries of safety and effectiveness (SSEDs) for similar legally marketed devices, may be helpful resources, and are available on our websites.[8] We strongly recommend that you make use of our online information and other available resources prior to submitting a Pre-Sub.

This guidance outlines clear recommendations for sponsors and for FDA staff and managers as well as expected timeframes for scheduling meetings. FDA intends to provide the best possible advice in accordance with the information provided, ensure it is captured accurately in the meeting minutes drafted by the sponsor, and commit to that advice unless the circumstances sufficiently change such that our advice is no longer applicable, such as when a sponsor changes the intended use of their device after we provide feedback. It is also our intention to hold timely meetings with appropriate staff and managers present, as resources permit. However, both our ability to provide advice and to hold timely meetings are dependent on our receiving the necessary information in advance of the meeting.

In addition, this guidance also describes the procedures that CDRH and CBER intend to follow when manufacturers, their representatives, or application sponsors request a meeting with review staff, either as the preferred method of feedback in response to a Pre-Sub, or to discuss to an existing

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http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm079448.htm

[4] Since CBER reviews submissions for drugs and biologics as well as medical devices, the program will be known as the Device Pre-Sub at CBER.

[5] Please see 21 CFR 812.3(m) (definition of significant risk device) and www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/default.htm.

[6] See CDRH Device Advice, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/default.htm

[7] CBER's Manufacturers Assistance and Technical Training Branch email; industry.biologics@fda.gov

[8] See United States Food and Drug Administration, Medical Devices, http://www.fda.gov/MedicalDevices/default.htm and Development & Approval Process (CBER) http://www.fda.gov/BiologicsBloodVaccines/DevelopmentApprovalProcess/default.htm

regulatory submission. This guidance also recommends how to prepare for meetings with FDA staff.[9]

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidance documents describe the agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in agency guidance documents means that something is suggested or recommended, but not required.

II. The Pre-Sub Program

A Pre-Submission is defined as a formal written request from an applicant for feedback from FDA to be provided in the form of a formal written response or, if the manufacturer chooses, a meeting or teleconference in which the feedback is documented in meeting minutes. A Pre-Submission is appropriate when FDA's feedback on specific questions is necessary to guide product development and/or application preparation.

The Pre-Sub is not a required submission and is entirely voluntary on the part of the sponsor. The Pre-Sub program is intended to allow applicants/sponsors the opportunity to obtain targeted FDA feedback in response to specific questions related to product development, including planned nonclinical evaluations, proposed clinical study protocols, or data requirements prior to making a submission to the Agency. Pre-Subs are not required prior to submission of an IDE or any premarket application, but are strongly encouraged. It is the applicant's decision whether or not to submit a Pre-Sub prior to submission of an IDE, 510(k), PMA, or HDE. However, early interaction with FDA on planned nonclinical and clinical studies and careful consideration of FDA's feedback may improve the quality of subsequent submissions and facilitate the development process for new devices.

A. When to Submit a Pre-Sub

Pre-Subs may be particularly helpful in the following circumstances, but are generally useful for early feedback on specific questions during submission preparation:

1. Before conducting clinical, nonclinical, or analytical studies, or submitting an IDE, or marketing application when:
    - the new device involves novel technology and it may be helpful to familiarize the FDA review team with the technology in advance of the submission;
    - the proposed indication will cause the device to be a "first of a kind" device;

[9] In certain circumstances, you may request a formal early collaboration meeting. For either Determination or Agreement Meeting requests, the subject of the cover letter should include: "Determination/Agreement Meeting." The scope and further procedures for these programs are described in the guidance entitled: "Early Collaboration Meetings Under the FDA Modernization Act (FDAMA)" at http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM073611.pdf.

- the new device is a multiplex device capable of simultaneously testing a large number of analytes;
- the new device is an in vitro diagnostic (IVD) device that contains a new technology, a new intended use, a new analyte, new clinical questions, complex data/statistical questions, and/or where the predicate of the reference method is unclear or uncertain;
- you desire FDA guidance on specific issues related to nonclinical study protocols and/or animal study protocols[10], before initiating your studies;
    - FDA input on your proposed testing is especially encouraged for studies that will have a long duration or for which there is no single clearly established consensus method for collecting the data;
- you desire FDA input on specific issues related to your planned clinical studies, especially if they involve complex or novel statistical approaches; and/or
- you desire FDA input on a clinical protocol before conducting a clinical study that does not require FDA review of an IDE, such as for a nonsignificant risk device or a study you plan to conduct entirely outside the US (OUS).

2. Before submitting a marketing application:

- to apprise the FDA review team on the particulars of the device and clinical study (if there have been changes since initiation of the IDE);
- to obtain our feedback on preferred data presentation and to ensure clarity with respect to our expectations regarding the elements to be included in the marketing application; and/or
- to gain insight into potential hurdles for approval or clearance (e.g., numerous protocol deviations, missing data, or a failed study endpoint).

B. The Pre-Sub Process

As noted, there are several points during the product development process when you may want to communicate with FDA. For example, before an IDE application, FDA may advise you on bench and animal protocols submitted in a Pre-Sub. In a subsequent Pre-Sub, you may request feedback on a planned clinical study protocol. In order to maintain continuity, all Pre-Subs related to a unique device/indication combination will be tracked as supplements to the original Pre-Sub. Meeting minutes and requests for clarification will be tracked as amendments to the initial request for feedback, whether in an original Pre-Sub or in a Pre-Sub supplement. However, the number of Pre-Subs submitted should be carefully considered to avoid confusion and unnecessary expenditure of time and resources on both industry's and FDA's part.

Resource constraints do not permit FDA to prepare or design particular study plans. The sponsor should propose a protocol, with a rationale for the chosen approach. Note that requests for a pre-review of data are not appropriate for the Pre-Sub program. However, if the data and conclusions

[10] FDA encourages sponsors to review all relevant horizontal and device-specific guidances prior to preparing a Pre-Submission.

are difficult to interpret, it may be appropriate to ask a specific question regarding the interpretation of preliminary results.

The Pre-Sub program is not meant to be an iterative process, (i.e., one in which FDA considers the same or similar information more than once). In general, the goal of the Pre-Sub program is to provide one-time advice on a particular topic, for example, a nonclinical or clinical study protocol. However, if you expect to submit more than one Pre-Sub to request feedback on additional topics for the same device, we suggest that your initial Pre-Sub contain an overview of your expected submissions, including general time frames, if known. This information would not be considered binding, but would aid FDA in planning for your subsequent Pre-Subs. Issues raised by FDA in response to a Pre-Sub do not have to be addressed or resolved in a subsequent Pre-Sub; however, it may be necessary to address such issues in the subsequent IDE or marketing application in order to meet the statutory and regulatory requirements for acceptance, filing, approval or clearance. Though there may be alternative ways to address the issues raised by FDA, because of the expenditure of agency and sponsor time and resources at the Pre-Sub stage, we encourage you to follow the approach recommended in response to your Pre-Sub if still applicable; otherwise, the agency and sponsor may have to expend additional resources.

Applicants should recognize that even though the agency may have already reviewed the study protocols/plans in a Pre-Sub, this does not guarantee approval or clearance of future submissions. Additional questions may be raised during the review of the future submission. Although Pre-Subs and the agency's advice are not decisional or binding on the agency or the applicant, it is FDA's intent to provide the best advice possible based on the information provided in the Pre-Sub and to remain consistent in our approach to regulating similar products.

C. What the Pre-Sub program is NOT

While the Pre-Sub program has been effective at answering specific protocol development and test planning questions, it is not an alternative to other review processes and procedures, nor should it be confused with other forms of informal FDA feedback. It is also not a substitute for conducting your own research and analysis of current medical device development practices.

There are other forms of FDA feedback to sponsors that are not considered Pre-Subs. However, if the requested feedback meets the criteria for a Pre-Sub, outlined above, FDA will contact the sponsor, and with the concurrence of the sponsor, may convert the request to a Pre-Submission. The following forms of feedback are not considered Pre-Subs:

- general information requests initiated through CDRH's Division of Small Manufacturers, International and Consumer Assistance (DSMICA) or CBER's Manufacturers Assistance and Technical Training Branch;

- general questions regarding FDA policy or procedures;

- meetings or teleconferences that are intended to be informational only, including, but not limited to, those intended to educate the review team on new device(s) with significant differences in technology from currently available devices, or to update FDA about ongoing

or future product development, without a request for FDA feedback on specific questions related to a planned submission (See Section IV.A. Informational Meetings below);

- requests for clarification on technical guidance documents, especially where contact is recommended by FDA in the guidance document.

  However, please note that the following requests will generally need to be submitted as a Pre-Sub in order to ensure appropriate input from multiple reviewers and management:

  - recommendations for device types not specifically addressed in the guidance document;
  - recommendations for nonclinical or clinical studies not addressed in the guidance document;
  - requests to use an alternative means to address recommendations specified in a guidance document;

- phone calls or email messages to reviewers that can be readily answered based on a reviewer's experience and knowledge and do not require the involvement of a broader number of FDA staff beyond the routine involvement of the reviewer's supervisor and more experienced mentors; or

- interactions requested by either the applicant or FDA during the review of a marketing application (i.e., following submission of a marketing application, but prior to reaching an FDA decision).

In addition, the Pre-Sub program should not be confused with other existing review processes. The Pre-Sub program is not:

- part of the interactive review process after a 510(k), IDE, PMA, or HDE, has been submitted. (For more information, please see the guidance entitled, "Interactive Review for Medical Device Submissions: 510(k)s, Original PMAs, PMA Supplements, Original BLAs, and BLA Supplements."[11,12]);

- a procedure for obtaining a determination respecting the jurisdictional assignment of a combination product, or the classification of a product as a drug, device, or biological product, or combination product (i.e., a Request for Designation (RFD)]. (Please see the Office of Combination Products web site for guidance on jurisdictional assignment and classification);

- a mechanism for obtaining a determination regarding the class in which a device has been classified or the requirements applicable to a device under the FD&C Act. While the

[11] Interactive Review for Medical Device Submissions: 510(k)s, Original PMAs, PMA Supplements, Original BLAs, and BLA Supplements
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089402.htm

[12] In some cases, an applicant or sponsor may wish to request a meeting or teleconference to further discuss deficiencies identified during the review of an application (see Section IV.C. Submission Issue Meetings).

potential regulatory pathway for your device may be a topic of discussion in a Pre-Sub interaction, device classification is accomplished in accordance with Section 513 of the Federal Food Drug and Cosmetic Act (FD&C Act). You can obtain additional information about how your device might be classified via Section 513(g) of the FD&C Act. To provide additional information regarding 513(g) requests, FDA has also issued a draft guidance entitled, "FDA and Industry Procedures for Section 513(g) Requests for Information under the Federal Food, Drug, and Cosmetic Act"[13];

- a mechanism to appeal a decision on a premarket submission (To provide information on appealing a decision, FDA has issued a draft guidance entitled: "Draft Guidance for Industry and Food and Drug Administration Staff – CDRH Appeals Processes,"[14] or for submissions made to CBER, see "Guidance for Industry: Formal Dispute Resolution: Appeals Above the Division Level" [15] and CBER SOPP 8005: Major Dispute Resolution Process [16]);

- a request for Evaluation of Automatic Class III Designation (de novo) classification or related inquiries (For information on the de novo process, see the guidance entitled, "Evaluation of Automatic Class III Designation, Guidance for Industry and CDRH Staff"[17]); or

- a determination meeting under Section 513(a)(3)(D) of the FDC Act to determine the type of valid scientific evidence necessary to show effectiveness in a PMA or an Agreement meeting under Section 520(g)(7) to reach agreement on an investigational plan, including a clinical protocol.

D. Pre-Sub Feedback

FDA feedback to a Pre-Sub can be provided in multiple ways, including through an in-person meeting, a teleconference, facsimile[18] or by email.[19] If FDA feedback will be through a meeting or

[13] FDA and Industry Procedures for Section 513(g) Requests for Information under the Federal Food, Drug, and Cosmetic Act
http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM209851.pdf

[14] Draft Guidance for Industry and Food and Drug Administration Staff – CDRH Appeals Processes
http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM284670.pdf. When final, this guidance will represent the Agency's current thinking on this topic.

[15] Guidance for Industry: Formal Dispute Resolution: Appeals Above the Division Level
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079743.pdf

[16] CBER SOPP 8005: Major Dispute Resolution Process
http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm109574.htm

[17] Evaluation of Automatic Class III Designation, Guidance for Industry and CDRH Staff
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/ImportingandExportingDevices/ucm080195.htm

[18] CBER SOPP 8113: Handling of Regulatory Faxes
http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm079472.htm

teleconference, at least 3 business days prior to the meeting, FDA will provide initial feedback to the applicant by email, which should include: written responses to the applicant's questions; FDA's suggestions for additional topics for the meeting or teleconference, if applicable; or, a combination of both. The written response may be a complete response to the applicant's question, or may consist of some initial feedback and note the need for further discussion in the meeting or teleconference. If all of the applicant's questions are addressed through the written responses to the applicant's satisfaction, FDA and the applicant can agree that a meeting or teleconference is no longer necessary and the written responses provided by email will be considered the final written feedback to the Pre-Submission. FDA will aim to provide feedback to a Pre-Sub within approximately 90 days, of receipt of a complete package (see Section III below).

FDA Feedback to a Pre-Sub

Our staff devotes significant time to the review of a Pre-Sub and preparation for a meeting or teleconference, if planned. As noted above, FDA feedback represents our best advice based on the information provided in the Pre-Sub and other information known at that point in time. However, FDA intends that feedback the Agency provides in response to a Pre-Sub will not change, provided that the information submitted in a future IDE or marketing application is consistent with that provided in the Pre-Sub and that the data in the future submission do not raise any important new issues materially affecting safety or effectiveness. Modifications to FDA's feedback will be limited to situations in which FDA concludes that the feedback given previously does not adequately address important new issues materially relevant to a determination of safety or effectiveness that have emerged since the time of the Pre-Sub. In such cases, FDA will acknowledge a change in our advice, will document clearly the rationale for the change, and the determination will be supported by the appropriate management concurrence.[20]

We recommend that if more than 1 year has passed since our last feedback on key clinical trial design elements with no submission to the agency, sponsors should contact the review branch to confirm that the previous advice is still valid.

We recommend that all submissions subsequent to a Pre-Sub interaction include a section that clearly references the previous communication(s) with FDA about the subject device (or similar device). The submission should include a reference to the Pre-Sub or Meeting Request number and any meeting minutes or written feedback provided. Further, to facilitate review, we recommend that the submission address how any previous feedback has been addressed within the current submission.

For recommendations that apply to Pre-Subs for specific submission types, please see the Appendix: Recommendations for Specific Types of Pre-Subs.

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[19] CBER SOPP 8119: Use of Email for Regulatory Communications http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm109645.htm. CBER generally provides such communications through secure email.

[20] For ODE, the CDRH SOP: Decision Authority for Additional or Changed Data Needs for Premarket Submissions should be followed: http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHReports/ucm279288.htm

III. Recommended Information for All Pre-Sub Packages

We recommend your Pre-Sub include the information below, organized as described.

A. Cover Letter

Please include a cover letter that clearly states the reason for the submission in the reference line (e.g., Pre-Sub for a 510(k), Pre-Sub for an IDE) and, for CDRH submissions, please clearly indicate that the submission is a Pre-Sub on the CDRH Premarket Review Submission Cover Sheet.[21] Use of the CDRH Premarket Review Submission Cover Sheet for submissions made to CBER is highly recommended.

For CDRH submissions, the addressee may be the appropriate branch or branch chief if the applicant knows where the subject device or similar devices are reviewed. For CBER submissions, the addressee may be the appropriate Office Director or Regulatory Project Manager where the subject device or similar devices are reviewed. The cover letter should contain complete contact information (i.e., the company name, address, contact person, phone number, fax number, and email address). In addition to describing the reason for the submission in the reference line, the cover letter should also clearly identify the name of the device and include the signature of the contact person, or other responsible party.

B. Table Of Contents

To facilitate ease of review, please include a table of contents at the beginning of your Pre-Sub showing items and page numbers. We strongly recommend the use of tabs or dividers between sections, and sequential numbering of the pages of your Pre-Sub package.

C. Device Description

Please provide sufficient information regarding the device description[22], which may include:

- pictures of the device (where applicable);
- engineering drawings (where applicable);
- physical, chemical and/or biological processes/principles used by the device to generate device output, if applicable
- physical and biological characteristics of the device output, if applicable;
- samples to demonstrate the use of the device (where feasible and appropriate);
- explanation of the user interface and/or how the device interacts with other devices or with the user (medical professional and/or patient);

[21] CDRH Premarket Review Submission Cover Sheet available at http://www.fda.gov/ForIndustry/UserFees/MedicalDeviceUserFeeandModernizationAct/ucm155274.htm

[22] For devices regulated by CBER, if the biologic output of the device is administered to the patient, then this output should be included in the device description section of the pre-sub package.

- explanation of the materials used in the device;
- a brief explanation of how the device is manufactured (where necessary);
- discussion of the mechanism of action and how the device and/or, if applicable, device output is used;
- for an IVD, detailed technical description of your device including instruments, reagents, components, software, principles of operation, and accessories (if there are changes to a previously cleared or approved device, then you should describe these changes);
- discussion of the scientific basis for development of the device or an explanation of expected clinical utility; and
- for a device to be submitted in a 510(k), any anticipated predicate and a comparison to the subject device.

In addition to pictures and a written description, other information about the clinical use of the device, such as a surgical technique guide or video of how the device is used in the clinical setting, may be helpful.[23]

D. Proposed Intended Use/Indications for Use

Please provide sufficient information regarding the proposed intended use/indications for use, which may include:

- identification of the disease or condition the device is indicated to prevent, mitigate, screen, monitor, treat, or diagnose;
- identification of the target population;
- part of the body or type of tissue to which applied or with which the device is interacting;
- frequency of use;
- physiological use; and
- statement of whether the device is intended for prescription and/or over-the-counter use.

For an IVD device, this information should include a detailed draft of the intended use of the device including the intended use population, the analyte/condition to detect, and the assay methodology (see Section F of Appendix A for more detailed information).

E. Previous Discussions or Submissions

Please summarize any previous discussions/submissions (including submission numbers) with the agency on this or a similar device.

[23] To submit a video, please contact the CDRH branch chief or division representative or the CBER Regulatory Project Manager for more information.

F. Overview of Product Development

Please provide an overview of the product development, including an outline of nonclinical and clinical testing either planned or already completed. However, please note that our review of a Pre-Sub will not address bench or clinical data that you have already collected.

If you intend to include complete copies of literature articles as part of this section, please try to include only those that are relevant to the questions you are asking. Additional articles can be provided in any subsequent marketing application or IDE.

G. Specific Questions

The Pre-Sub should include specific questions regarding review issues relevant to a planned IDE, or marketing application (e.g., questions regarding pre-clinical and clinical testing protocols or data requirements) as our advice will be guided by your questions and may not identify all submission requirements. The Appendix of this guidance contains sections specific to IDE, 510(k), PMA, and HDE that list examples of questions appropriate to each submission and application type.

H. Mechanism for Feedback

You should specify how you prefer FDA to provide the feedback you are seeking. You may request our feedback through an in-person meeting, a teleconference, facsimile, or by email. Please note that FDA will ultimately decide the means of communicating the feedback, but will consider the desired mechanism requested in the Pre-Sub. If we provide feedback through a meeting or teleconference, the final meeting minutes will be considered FDA's formal written feedback. See Section IV below for additional items to include in your Pre-Sub.

I. Other Logistical Information

In general, a Pre-Sub should be a clear and concise document that includes the relevant background information and specific questions for FDA. However, if the Pre-Sub is for a nonsignificant risk device, IDE exempt device, or a study you plan to conduct outside the US (OUS), you may submit the entire protocol.

Please be advised that your Pre-Sub should be written in the English language. Any material in a foreign language should be accompanied by an accurate and complete English translation.

For CDRH-regulated products, you should send three (3) copies of your Pre-Sub to the address below. We strongly encourage you to submit an electronic copy,[24] in which case you may submit only 2 hard copies. You may also wish to contact the branch chief or division representative regarding submission of any other materials.

U.S. Food and Drug Administration
Center for Devices and Radiological Health

[24] For information about preparing an electronic copy for submission to CDRH, see http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/ucm134508.htm.

Pre-Sub Document Mail Center – WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

For products regulated in the Center for Biologics Evaluation and Research (CBER), you should send three (3) copies of your Device Pre-Sub to the address below. We strongly encourage you to submit an electronic copy in which case you may submit only two (2) hard copies. Instructions for providing an electronic copy to CBER are included in CBER Guidance[25] and CBER SOPPs.[26]

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center (HFM-99)
1401 Rockville Pike, suite 200N
Rockville, MD 20852-1448

Note: Neither Center can accept Pre-Sub packages by email, although we strongly recommend submission of an electronic copy as one of the official 3 copies.

For submissions to CDRH, on the business day that the Pre-Sub is received by the Document Mail Center (DMC), the Pre-Sub is assigned a unique tracking identifier by the DMC.[27] Any future communications regarding your Pre-Sub should include this unique Pre-Sub identifier. The Pre-Sub contact will be mailed an acknowledgement letter that contains the unique tracking number and date received by the DMC. The acknowledgement letter is also sent via fax or via e-mail as provided in your cover letter.

Because of organizational differences between CBER and CDRH, the process described in the preceding paragraph is not applicable to submissions sent to CBER. Please consult CBER SOPP 8114: Administrative Processing of Documents R ceived Prior to Submitting Investigational or Marketing Applications (Pre-Application).[28]

IV. All Meetings with CDRH and CBER Staff

The meetings with industry and other sponsors described in this guidance allow for an open discussion and exchange of technical, scientific, and regulatory information. These meetings can

[25] Guidance for Industry: Providing Regulatory Submissions in Electronic Format - General Considerations; www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072390.pdf.

[26] SOPP 8110: Submission of Paper Regulatory Applications to CBER; http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm079467.htm

[27] CDRH assigns each Pre-Sub a unique tracking identifier; beginning with the letter "I" followed by the last two digits of the year, followed by 4 digits that are assigned sequentially beginning on January 1st. For example, the first Pre-Sub logged in on January 1, 2008, was assigned "I080001."

[28] CBER SOPP 8114: Administrative Processing of Documents Received Prior to Submitting Investigational or Marketing Applications (Pre-Application) http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm079476.htm

help build a common understanding of FDA's views on clinical, nonclinical, or analytical studies related to an IDE or marketing application.

Meetings requested of CDRH and CBER typically fall into one of three categories – Informational Meetings, Pre-Submission Meetings, and Submission Issue Meetings. This guidance does not address Agreement and Determination Meetings or Appeal Meetings; in addition, this guidance does not address the Interactive Review Process.

A. Informational Meetings

A sponsor or applicant may request a meeting in which the intent is to share information with FDA without the expectation of feedback. Specifically, an Informational Meeting may be appropriate to:

- Provide an overview of ongoing device development when there are multiple submissions planned within the next 6-12 months, or
- Familiarize the review team about new device(s) with significant differences in technology from currently available devices.

The intent of an Informational Meeting is for FDA staff to be in a listening mode. Such meetings can be helpful to familiarize reviewers, especially new reviewers, and can also assist the Branch in resource planning for upcoming submissions. However, while our staff will review the materials provided at the time of the meeting request and may ask clarifying questions during the meeting, they will not be prepared to provide any feedback. If you are seeking feedback on any aspect of this information, you should submit a Pre-Sub and request a Pre-Sub Meeting.

FDA plans to accept requests for Informational Meetings when one of the above factors is met and as resources allow.

FDA will aim to schedule an Informational Meeting within 90 days of receiving the meeting request. To request such a meeting, you should submit a meeting request, clearly identified as an Informational Meeting Request in the cover letter, along with complete background information to one of the addresses listed in Section III.I (above).

See Section D below for recommendations regarding the content of your meeting request.

You should send three (3) copies of the appropriate background information for your requested meeting. This information will be captured and tracked as an Informational Meeting Request. We strongly encourage you to submit an electronic copy, in which case you may submit only 2 hard copies. You may also wish to contact the branch chief or division representative regarding submission of any other materials.

B. Pre-Sub Meetings

A sponsor or applicant may request a meeting as the preferred mechanism of feedback for a Pre-Sub. The intent of this meeting is for FDA staff to provide feedback on specific questions identified in the Pre-Sub. See Sections II and III above for more information on the Pre-Sub program.

Within 14 calendar days of receipt of a request for a meeting or teleconference, FDA will determine if the request meets the definition of a Pre-Sub Meeting, and will inform the applicant if it does not meet the definition. A determination that the request does not meet the definition of a Pre-Sub Meeting will require the concurrence of the branch chief and the reason for this determination will be provided to the applicant. If the request meets the definition of a Pre-Sub Meeting, FDA and the applicant will set a mutually agreeable time and date for the meeting.

FDA will aim to schedule a Pre-Sub Meeting within 75 days, but no longer than 90 days, of receipt of the complete Pre-Sub. In rare cases where there is an urgent public health issue (e.g., changes to an ongoing study are necessary to address an identified safety concern), we will aim to schedule the meeting within 21 days. If the need for such an urgent meeting can be identified earlier than 21 days from the desired meeting date, but full background information is not available at the time of your meeting request, this information can be provided as an amendment to the Pre-Sub. This amendment should be received no later than 21 days in advance of the urgent meeting to ensure that FDA staff have adequate time for review. If the information is not received 21 days in advance of your meeting date, we may contact you to reschedule the meeting for a later date.

At least 3 business days prior to the meeting, FDA will provide initial feedback to the applicant by email, which should include: written responses to the applicant's questions; FDA's suggestions for additional topics for the meeting or teleconference, if applicable; or, a combination of both. The written response may be a complete response to the applicant's questions, or may consist of some initial feedback and note the need for further discussion in the meeting or teleconference. If all of the applicant's questions are addressed through prior written responses to the applicant's satisfaction, FDA and the applicant can agree that a meeting or teleconference is no longer necessary and the written responses provided by email will be considered the final written feedback to the Pre-Submission.

To request a Pre-Sub Meeting, you should submit a Pre-Sub, clearly noting that your preferred mechanism of feedback is a Pre-Sub Meeting in the cover letter described in Section III.A above, along with complete background information, to the address listed in Section III.I above.

See Section III above as well as Section D below for recommendations regarding the content of your Pre-Sub.

You should send three (3) copies of the appropriate background information for your requested meeting. This information will be captured and tracked as a Pre-Sub. We strongly encourage you to submit an electronic copy, in which case you may submit only 2 hard copies. You may also wish to contact the branch chief or division representative regarding submission of any other materials.

C. Submission Issue Meetings

A sponsor or applicant may request a Submission Issue Meeting to discuss deficiencies identified during premarket review of a 510(k), de novo, IDE, HDE, or PMA application, whether these deficiencies were communicated in writing (e.g., additional information, major deficiency, or not approvable letter) or through email, telephone, or fax (e.g., telephone hold). Such a meeting is not

intended for pre-review of planned responses, but instead to provide clarification of FDA's questions or to discuss an approach to responding to complex issues.[29] Note that this guidance does not address Day 100 meetings for original PMAs and Panel-track PMA Supplements.

FDA will aim to schedule Submission Issue Meetings within 21 days of the receipt of the meeting request. For CDRH submissions, such requests may be submitted via email to the lead reviewer of the application or to the applicable manager, with hard copies submitted to the Document Mail Center as outlined below. For CBER submissions, please refer to CBER SOPP 8119: Use of Email for Regulatory Communications. [30]

The background information should be limited to the information necessary to discuss the deficiencies at issue (i.e., mere repetition of data from your IDE or marketing application is not useful). This information will be captured as a separate submission and linked to the submission under review through our electronic tracking system and in the lead reviewer's memoranda.

To request a Submission Issue Meeting, you should submit a meeting request, clearly identified as a request for a Submission Issue Meeting in the cover letter, along with appropriate background information to the address listed in Section III.I above.

See Section D below for recommendations regarding the content of your meeting request.

You should send three (3) copies of the appropriate background information for your requested meeting. We strongly encourage you to submit an electronic copy, in which case you may submit only 2 hard copies. You may also wish to contact the branch chief or division representative regarding submission of any other materials.

D. Content of a Request for a Meeting with FDA Staff

Adequate meeting preparation is essential to a productive meeting. When you provide complete background information for the meeting in a timely manner, we are able to thoroughly review the information and ensure that the appropriate FDA staff members have the opportunity to comment. This enhances the quality of the information exchange during the meeting.

Meeting Request

Your request for a meeting should include the type of meeting you are requesting – Informational Meeting, Pre-Sub Meeting, or Submission Issue Meeting.

For a Pre-Sub Meeting, your meeting request should consist of a complete Pre-Sub package (see Section III. Recommended Information for All Pre-Sub Packages).

[29] A request for a Submission Issue Meeting does not take the place of a formal response to the relevant premarket application and as such will not impact the requirement that a formal response be submitted within a specified time limit to avoid the application being considered withdrawn.

[30] SOPP 8119: Use of Email for Regulatory Communications http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm109645.htm

For an Informational Meeting or Submission Issue Meeting, your request should include:

- a reference to the premarket submission number or other related documents, if any;
- a brief statement describing the purpose, scope, or objectives of the meeting;
- a complete description of your device, including the intended use/indications for use for the device (Note: A thorough background package allows less meeting time to be spent on background information and more time to be allotted to discussion of questions.);
- a proposed agenda, including the estimated time for each agenda item; and
- focused questions for which you are seeking guidance from FDA, if applicable.

For all meeting types, your request should include:

- the meeting format you are requesting (i.e., in-person or by teleconference);
- three (3) or more preferred dates and times when you are available to meet using the guidelines above for scheduling;
- contact information, including contact name, telephone number and an email address;
- the planned attendees, including each attendee's position, or title, and affiliation. If you have not yet identified all of your attendees, you should indicate the type of subject matter experts you plan to invite so that we can ensure appropriate FDA experts are in attendance. Please note foreign visitors meeting in an FDA facility require advanced security clearance. See Section F "Security Screening" below for additional information on how to request security clearance for Foreign Nationals; and
- a list of any audiovisual equipment you will need, such as conference phone or LCD projector.

Your meeting request should be concise, yet contain sufficient information to allow FDA to address the focused questions in your meeting request. The meeting request should not be a complete premarket submission. If your meeting is related to deficiencies identified during review of a premarket submission, you do not have to resubmit information contained in your initial submission, but you should clearly identify which deficiencies you wish to discuss and the questions or clarifications you would like FDA to address.

You should propose the duration of the meeting you are requesting. In our experience, one (1) hour is adequate for most meetings. If you believe that more than one (1) hour is needed, please provide a rationale for the duration you propose. You should also refer to the rationale and confirm the duration requested when the division contact person schedules your meeting.

We recommend that your agenda allocate the last ten (10) minutes of the meeting for summarizing the discussions and any next steps or action items.

E. FDA Response to Meeting Requests

After we review your meeting request and background information, we will contact you to schedule your meeting. Factors such as your suggested dates and times, the availability of FDA staff, the completeness of your background information, and the complexity of the issues can affect the scheduling of your meeting. In certain limited cases, we may determine that a meeting is not necessary or appropriate, and will contact you to discuss the reasons for this conclusion.

1. Reviewing the Meeting Request

Generally, the manager of the respective premarket review group will consider your request and assign it to a meeting coordinator or lead reviewer in the group or division. If your background information is not complete, the meeting coordinator or lead reviewer will notify you of the additional information needed before the meeting can be scheduled. If a substantial amount of the information needed to facilitate scheduling of the meeting is missing, we will close the Pre-Sub or meeting request until a supplement with the additional information is received.

If your background information is complete, the meeting coordinator or lead reviewer will contact you to discuss scheduling your meeting. Although in-person meetings may have some advantages compared to teleconferences, in some cases in-person meetings may take longer to schedule due to conference room availability. When possible and appropriate, we encourage you to consider a teleconference instead of an in-person meeting.

For Pre-Sub meeting or teleconference requests, within 14 calendar days of receipt we will determine if the request meets the definition of a Pre-Sub Meeting, and will inform you if it does not meet the definition. FDA will also determine if the request necessitates more than one meeting or teleconference. A determination that the request does not meet the definition of a Pre-Sub Meeting will require the concurrence of the branch chief and the reason for this determination will be provided to you. If the request meets the definition of a Pre-Sub Meeting, we will work with you to set a mutually agreeable time and date for the meeting following the guidelines below. If the request does not meet the definition of a Pre-Sub Meeting, but instead meets the definition of an Informational Meeting or Submission Issue meeting, FDA will notify you and proceed according to the applicable timelines in Section IV.A. or Section IV.C., respectively.

2. FDA Attendees

We will always attempt to ensure the appropriate FDA staff are present at your meeting. Generally, our attendees will include members of the FDA review team (including consultants from other Offices or other Centers), and the first line manager. As appropriate, members of division management and the Program Operation Staff (POS) may also attend.

You can help to ensure that appropriate FDA staff are present by suggesting that certain types of experts attend, depending upon the specific questions or issues that you wish to address. For example, if statistical issues are included in your focused questions, it is appropriate to suggest that our statistician attend.

3. FDA Facilities

For an in-person meeting, the meeting coordinator or lead reviewer will reserve the room and arrange for any audiovisual equipment you may have requested. For teleconferences, you should provide a call-in number. Please note visitors are not allowed access to any FDA/HHS information technology systems. This includes attaching USB cables, thumb drives or any other equipment to any FDA/HHS equipment.

4. Meeting Confirmation

The FDA meeting coordinator or lead reviewer will inform you of the date and time of the meeting. The meeting coordinator will also inform you of the date by which you should submit any supplemental background information, if applicable.

5. Supplemental Background Information

To hold a productive meeting, we need adequate time to review your background information, schedule and conduct an internal pre-meeting to ensure all appropriate parties have had time to review, comment, and possibly follow up on any issues prior to your meeting. Therefore, as noted above, it is very important that you provide complete background information at the time of your initial meeting request. If you wish to supplement your background information package with any new or modified information after this date, we may have to reschedule the meeting or delay our feedback on certain discussion topics related to the new or updated information. While the importance of a complete background package cannot be overstated, it should also be noted that submission of extraneous information can be counterproductive. Please keep your background information targeted and focused on the questions at hand.

We expect that your presentation slides contain the same content as provided in the background information. You should provide these to us electronically (e.g., in Microsoft PowerPoint) at least two (2) business days before the meeting. This will allow adequate time to send the presentation to any of our staff who will be participating remotely. You may also choose to bring hard copies of your slides to the meeting, to facilitate our review. If your background material is captured in slide format only, your slides should be submitted at the time of the meeting request. If not provided with the initial meeting request, the presentation slides should not contain significant modifications or additional information as FDA would not be prepared to discuss this information. In certain cases this may result in the need to reschedule the meeting.

F. Security Screening

For meetings with CBER outside of the White Oak campus, our meeting coordinator or lead reviewer will provide you with all of the details necessary for you to enter our facilities. In general, you will be greeted in the lobby of the building and escorted to the meeting room.

For meetings on the White Oak campus, our meeting coordinator or lead reviewer will provide the building's security personnel with a list of your attendees at least one (1) business day before the meeting with the following information: name of visitors; date and time of visit; location of visit; name and phone number of the FDA point of contact. On the day of your scheduled meeting, we recommend that you arrive at our facility with sufficient time to undergo security screening and to set-up any audio-visual equipment before the meeting is scheduled to begin. However, as you will need to wait in the security area until an FDA contact can escort you to the meeting room; please do not plan to arrive more than 30 minutes in advance of your meeting.

Upon arrival at White Oak, the security personnel will announce your arrival by calling the FDA contact. All visitors must present a valid government-issued ID upon check-in and be escorted by an

FDA employee at all times. The FDA contact will escort your group to the meeting and, following the meeting, will be responsible to see you out of the building.

All non-U.S. citizens attending a meeting in an FDA facility are subject to additional security screening. For each non-U.S. citizen, you should complete the Foreign Visitors Data Request form[31] and submit the completed form to the meeting coordinator or lead reviewer ten (10) days prior to the meeting date. The CDRH International Visitor Coordinator will review the forms for completion, forward for security clearance and notify the meeting coordinator or lead reviewer once security has been approved.

G. During the Meeting

To make the most of limited resources, your meeting will start and end promptly.

The FDA meeting coordinator or lead reviewer will request that all attendees complete a sign-in sheet as part of the record of the meeting. In general, you should have a member of your team assigned to take meeting minutes, to be provided for FDA review following the meeting. The meeting minutes should be sufficiently detailed to ensure a mutual understanding of the major action items. Following the meeting, FDA's final version of meeting minutes will be considered the official meeting minutes, see "Activities after the Meeting" below. Industry attendees are not permitted to record the meeting by audio or video means.[32]

We recommend that you limit your formal presentation to no more than one-third of the allotted meeting time and focus your presentation on the scientific, regulatory, and administrative issues you wish to discuss with us. FDA will have thoroughly reviewed and discussed all of the background information submitted prior to the meeting, so it is not necessary to repeat the information included in your pre-meeting materials. This will allow sufficient time for discussion of the substantive issues. In the interest of time, if you want to make us aware of your company's history, business plan, or the current stage of development of your device, you should include this information in the background package rather than presenting it during the meeting.

We recommend that during the last ten (10) minutes of Pre-Sub or Submission Issue meetings, a summary of FDA's feedback and any action items be briefly reviewed to ensure that both parties have a clear understanding.

Please note that in most cases we are able to respond only to questions or issues that were included in your meeting request or background information. Usually we will not be able to discuss, or comment, on new information that is presented at the meeting and not included in the background information. This is because our staff need adequate time to thoroughly review, comment on, and

[31] See Foreign Visitors Data Request form: www.fda.gov/downloads/Drugs/NewsEvents/UCM167023.doc.

[32] CDRH and CBER policy is not to allow outside parties to record (by audio or video) meetings with staff in order to prevent interference with the free exchange of information. In accordance with 21 CFR Sec. 10.65(e), which addresses the issue of recording general meetings with outside parties, the authority to record meetings resides with the agency staff, not the outside party.

discuss any new information before the meeting.

You should also recognize that our views expressed during a meeting are based only on information made available to us before, and clarified during, the meeting. If circumstances later change, or new information becomes available following the meeting, we recommend that you contact the review group to discuss the new information and any impact it may have on our advice.

H. Activities after the Meeting

If requested, a copy of the attendance sign-in sheet will be provided to you at the end of the meeting.

Following the meeting or teleconference, you should develop draft minutes and provide the draft minutes via email to FDA within 15 calendar days of the meeting. The minutes should summarize the meeting discussions, document how substantial or complex issues were resolved, and include agreements and any action items. FDA will provide any edits to the draft minutes to you via email in a timely manner (generally within 30 days). These minutes will become final 15 calendar days after you receive FDA's edits, unless you indicate to the lead reviewer or the regulatory project manager[33] via email that there is a disagreement with how a significant issue or action item has been documented. In this case, in a timely manner, we will set up a mutually agreeable time for a teleconference to discuss that issue. At the conclusion of that teleconference, in a timely manner, FDA will finalize the minutes either to reflect the resolution of the issue or note that this issue remains a point of disagreement. This version will be considered the official meeting minutes. The teleconference is intended to address disagreements about the content of the minutes. It is not intended to address differences of opinion with respect to the regulatory or scientific advice provided to the sponsor. Such differences of opinion sho ld be addressed in additional Pre-Sub meetings if both the applicant/sponsor and FDA believe that further discourse on such an issue would be productive.

I. Future Submissions

Issues raised by FDA in a meeting do not have to be addressed or resolved in a subsequent meeting or Pre-Sub; however, it may be necessary to address such issues in the subsequent IDE or marketing application in order to meet the statutory and regulatory requirements for acceptance, filing, approval or clearance. Though there may be alternative ways to address the issues raised by FDA, because of the expenditure of agency and sponsor time and resources at the Pre-Sub stage, we encourage you to follow the approach recommended in response to your Pre-Sub if still applicable; otherwise, the agency and sponsor will have to expend additional resources.

[33] For meetings with CBER, communication should be directed to the regulatory project manager.

Appendix

Recommendations for Specific Types of Pre-Subs

A. Pre-Sub for an IDE Application

The IDE regulations (21 CFR Part 812) require that Significant Risk (SR) device studies follow all of the IDE regulations, and have an IDE application approved by FDA.

In general, a SR device is defined [21 CFR 812.3(m)] as an investigational device that:

- Is intended as an implant and presents a potential for serious risk to health, safety, or welfare of a subject;
- Is purported or represented to be for use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;
- Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or
- Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

Studies of some devices, particularly certain in vitro diagnostics, are exempt from most of the IDE requirements of 21 CFR Part 812,[34] but must meet all other requirements of 21 CFR 812.819(c) as well as Parts 50 and 56. For additional information on in vitro diagnostic device studies, please refer to the guidance "In Vitro Diagnostic (IVD) Device Studies – Frequently Asked Questions."[35]

Although clinical studies conducted outside the US (OUS) are not subject to FDA regulation, we recommend Pre-Subs for certain OUS studies (refer to Part B of this appendix). If you plan to submit the results of an OUS study to FDA in a marketing application (i.e., 510(k), HDE, PMA or BLA), we are available to advise you about questions related to protocol design or study plans for these studies.

For more information about SR, Nonsignificant Risk (NSR), and exempt studies, please also review the "Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors – Significant Risk and Nonsignificant Risk Medical Device Studies."[36] If a sponsor would like FDA to evaluate whether a study is an SR, NSR or exempt study, they may submit a Pre-Sub, and FDA will issue a study determination letter. The subject line of the cover letter should state "Pre-Sub – Study

[34] See 21 CFR 812.2(c)(3).

[35] "In Vitro Diagnostic (IVD) Device Studies – Frequently Asked Questions." http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071230.pdf .

[36] "Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors - Significant Risk and Nonsignficant Risk Medical Devices Studies." http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126418.pdf

Determination Request," and should be accompanied with information about the devices being used in the study and a draft/outline of the study protocol.

1. When to Submit a Pre-Sub for an SR Device Study Requiring an IDE Application

Receiving and incorporating FDA feedback on various elements of a future IDE submission, such as the proposed study design or statistical analysis plan, can facilitate the IDE review process and reduce the number of review cycles needed to reach full IDE approval.

You may submit a Pre-Sub at any time prior to submitting your IDE. Typically, the most appropriate times to submit a Pre-Sub related to an IDE include:

- prior to initiating critical animal or bench testing;
- prior to requesting a feasibility study; or
- prior to initiating a pivotal trial.

A Pre-Sub for an IDE can also be useful to discuss nonclinical bench and animal testing plans, especially if the proposed testing is unusual or if the testing or study results are critical to the approval of the IDE application (e.g., an animal study intended to assess a critical safety question prior to use in human subjects).

After the IDE has been submitted, a Pre-Sub may be appropriate if you have conducted a feasibility study and would like advice during the planning phase of any subsequent pivotal trial protocol, or if significant changes to device or trial design are being contemplated.

2. Content of Pre-Sub for an SR Device Study Requiring an IDE Application

The Pre-Sub should contain sufficient background information to allow us to answer your specific questions. In addition to the information cited in Section III above, please consider whether the information below will be useful for providing advice on your IDE.

<u>Planned Nonclinical Testing</u>

Types of nonclinical testing for which you may want to seek feedback include:

- the rationale for your test strategy based on your risk analysis
- bench testing (such as biocompatibility, mechanical, electrical safety, electromagnetic compatibility (EMC), wireless compatibility, magnetic resonance (MR) compatibility, or software)
- animal studies.

If your questions pertain to your nonclinical testing, we recommend that you provide a concise summary of the test plan that includes:

- an identification of the objective or purpose of the test
- the sample size and statistical methods

- a summary of the test methodology (if you are following a recognized standard, include the name of the standard and year of publication)
- the acceptance criteria and a rationale for the selection of these criteria.

Clinical Protocol

The most common reason for submitting a Pre-Sub for an IDE is to seek advice on major elements of a clinical trial design, including:

- target patient population
- sample size
- type of control
- statistical analysis plan
- study endpoints
- length and type of follow-up.

If your questions pertain to aspects of your clinical trial design, you should submit at least an outline of the trial design; however, if you are seeking very specific advice, more detailed information may be needed (e.g., details of the statistical analysis plan).

3. Examples of Specific Questions for an IDE Pre-Sub

Your Pre-Sub should include specific questions. These questions provide the framework for our response. Examples of specific questions for an IDE may include:

- Are the nonclinical study protocols (bench or animal) sufficient to allow for the collection of data from which conclusions about device safety to support initiation of a clinical study can be drawn?
- Are the primary and/or secondary endpoints appropriate for the proposed indication for use?
- Are the proposed trial design and selected control group appropriate?
- Are the proposed sample size calculation method and related elements of the statistical analysis plan appropriate for the proposed clinical study?
- Do you have any concerns about whether the proposed follow-up period is adequate for the proposed clinical study?

4. Examples of general questions that are NOT conducive to a productive discussion

- Does FDA have any comments on the nonclinical test results?

- What are clinically meaningful outcomes for the device, and what is the best way to analyze them?

- How large should the sample size be?

- Does the FDA agree that the proposed clinical study protocol is adequate to support the safety and effectiveness of the device in a marketing application?

- Does the FDA agree that the clinical results provided in the background package for the meeting are sufficient to support the safety and effectiveness of the device in a marketing application?

B. Pre-Sub for a NSR, Exempt, or OUS Study

1. When to Submit a Pre-Sub for an NSR device, Exempt Diagnostic device, or OUS Study

Because FDA approval of an IDE is not required to conduct clinical studies of NSR or exempt diagnostic devices, or for studies located outside of the US (OUS), FDA is generally not involved in evaluation of the protocols. In these cases, sponsors will generally have limited opportunities to interact with the FDA prior to submission of a marketing application; therefore, a sponsor may choose to submit a Pre-Sub to help identify deficiencies that could preclude approval or clearance of a future marketing application. The appropriate time to submit a Pre-Sub for an NSR device, exempt diagnostic device, or OUS device study is after the protocol has been drafted but prior to requesting IRB approval for the study. Refer to Section F for more detailed information related to Pre-Subs for IVDs.

2. Content of Pre-Sub for an NSR, Exempt Diagnostic or OUS Study

Your cover letter should describe the specific type of Pre-Sub in the reference line (e.g., Pre-Sub for an OUS study). The Pre-Sub should contain the same information outlined above for a Pre-Sub for an SR Device Study Requiring an IDE Application (A.2).

3. Examples of Specific Questions for a Pre-Sub for an NSR, Exempt Diagnostic, or OUS Study

The questions appropriate to a Pre-Sub for an NSR, exempt diagnostic, or OUS study are generally the same questions appropriate for any clinical study. Please refer to the examples of specific questions in Section A.3. Pre-Sub for an IDE Application.

C. Pre-Sub for a 510(k)

1. When to Submit a Pre-Sub for a 510(k)

The advice FDA provides prior to submission of a 510(k) may be a highly effective tool in streamlining our review and determination regarding substantial equivalence, as our advice can aid in identifying planned testing that may be unnecessary or additional testing that we will need to review in the 510(k).

The timing of your Pre-Sub for a 510(k) should be reflective of your planning needs. It is advisable to submit a Pre-Sub request for a device subject to 510(k):

- prior to your initiation of critical or resource-intensive bench tests or animal or clinical studies; or
- if you know clinical data will be needed to support your 510(k), but have not yet interacted with FDA about the type of data needed (and/or the most appropriate reference method for an in vitro diagnostic device), and you know the study will not require an IDE, so there will not be any other opportunity for FDA to review the protocol; or
- if your planned 510(k) submission might raise unusual or atypical issues that warrant preliminary discussion with FDA.

As described in Section II, if you have questions regarding the formal classification of your device, or the lead Center for a combination product, a Pre-Sub is not generally appropriate. Instead, these questions are more appropriately managed through either the 510(k) program or contact with the Office of Combination Products.[37]

2. Content of a Pre-Sub for a 510(k)

The Pre-Sub should contain sufficient information for FDA to provide advice to your specific questions. In addition to the information suggested in Section III of this guidance, we suggest that you also provide the following.

Proposed Predicate Devices

The 510(k) review process focuses on the comparison of a proposed device with a predicate device in terms of indications for use, technological characteristics, and, as appropriate, performance testing. As a result, you should provide a summary of the predicate device(s) you plan to use for your comparison of these characteristics, along with the indication(s) for use and technology of the device you would like to market (i.e., draft of your labeling).

For each predicate device you identify, we suggest you provide:

- the predicate device trade name, including model, if available;
- the 510(k) number under which the predicate device was cleared;
- the classification of the predicate device;[38] and
- a comparison with the proposed device in terms of indications for use, technological characteristics, and performance testing.

[37] For questions about whether CDRH, CDER, or CBER is the lead Center for review of your combination product please see the guidance entitled, "How to Write a Request for Designation (RFD)," http://www.fda.gov/RegulatoryInformation/Guidances/ucm126053.htm.

[38] The identification of the classification and predicate should include the product code (e.g., DXN) and classification regulation (name and section) for the predicate device (e.g., "Noninvasive blood pressure measurement system," 21 CFR 870.1130).

Please note that a final determination about the suitability of a proposed predicate device will not be made until the submission and review of your 510(k).

Performance Testing

A summary of performance testing may include the following:

- bench testing (such as biocompatibility, mechanical, electrical safety, electromagnetic compatibility (EMC), wireless compatibility, magnetic resonance (MR) compatibility, or software, and comparison to the predicate device);
- animal studies (in vivo and histopathology); and
- clinical studies.

Please clearly distinguish any testing that has already been conducted from testing you plan to conduct in the future.

Information you may consider for inclusion with respect to performance may include a concise summary of the test plan that includes:

- identification of the objective or purpose of the test;
- explanation of the sample size and statistical methods, as applicable;
- summary of the test methodology (if you are following a recognized standard, include the name of the standard and year of publication)
- explanation of study endpoints; and
- explanation of study acceptance criteria.

As a reminder, test results and data do not need to be submitted in the Pre-Sub, as FDA will not make a final determination regarding substantial equivalence on the basis of the Pre-Sub. This comprehensive evaluation will only be made during the review of the 510(k) submission.

3. Examples of Specific Questions for a 510(k) Pre-Sub

Examples of questions that may be appropriate to consider in a 510(k) Pre-Sub are given below according to topic.

Biocompatibility

- In addition to the biocompatibility testing recommended for the type and duration of tissue contact defined by FDA's G95-1 Bluebook Guidance and ISO 10993-1, what other device-specific biocompatibility testing may be necessary to adequately evaluate the biocompatibility of my device?
- Is our justification for not conducting carcinogenicity studies adequate?

Bench and Animal Testing

- Does FDA concur it is appropriate to test only the smallest and largest sizes of my device in comparison to a predicate device when I plan to market at least ten (10) different sizes that differ in dimensions?

- Does FDA concur with our worst-case rationale for this device?

- Is the animal model I propose appropriate for testing my device?

Software

- Is a "moderate level of concern" the appropriate level of concern for my software?

Human Factors Evaluation

- Is my planned approach to human factors assessment appropriate for the intended use of my device?[39]

Clinical Evaluation

- Is it advisable to conduct a clinical evaluation of my device or is the battery of bench and animal testing I propose likely to be adequate? (In some cases, FDA may not be able to assess whether bench and animal data are sufficient in lieu of clinical data until a review of the nonclinical testing has been completed.)

- If clinical data are needed for my device, are the proposed trial design and selected control group appropriate?

Predicate Device

- Are there concerns with the predicate device proposed?

D. Pre-Sub for a PMA

1. When to Submit a Pre-Sub for a PMA

FDA strongly recommends a Pre-Sub prior to the submission of any PMA so that we can relay important considerations for filing, formatting, electronic data, etc. in addition any device-specific discussions. A Pre-Sub for a PMA should be submitted no less than ninety (90) days prior to submission of the PMA. This will afford time for the agency to provide feedback on the specific questions and for the applicant to modify the planned PMA submission accordingly.

[39] Please see FDA's guidance entitled: "Medical Device Use – Safety: Incorporating Human Factors Engineering into Risk Management," http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094461.pdf , which will be superseded by "Draft Guidance for Industry and Food and Drug Administration Staff - Applying Human Factors and Usability Engineering to Optimize Medical Device Design" when final. http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259748.htm.

2. Content of a Pre-Sub for a PMA

The Pre-Sub should contain sufficient information so that FDA can provide advice on your specific questions related to the format and content of your upcoming PMA application. In addition to the information suggested in Section III of this guidance, a PMA Pre-Sub should address the following, although not all topics may need to be addressed in depth, if at all.

General Considerations

A Pre-Sub for a PMA device should include:

- a discussion of any device specific or general guidance documents you plan to use to prepare the PMA;
- a discussion of your rationale for omitting any element listed in CDRH's PMA filing checklist;[40]
- a discussion of how each advisory or "future PMA concern" identified in your IDE approval or conditional approval letter(s) will be addressed in your PMA;
- identification of manufacturing sites and when those sites will be ready for inspection;
- a discussion of any issues raised in a previous Pre-Sub and confirmation that those issues have been addressed and if any alternate means are utilized, a brief discussion of those means;
- a discussion of your rationale for qualification for expedited review, if you plan to request expedited status in your submission;[41]
- if you have a preference for whether your PMA is reviewed by an Advisory Committee, that preference and rationale;
- a summary of any changes in the device or the intended use or patient populations since either the IDE approval or previous discussions through a Pre-Sub if no IDE was required, and reasons for any changes, such as:
  - a discussion of human factors studies, lessons learned from the clinical study, or other information gained since the initiation of the clinical study that led to such

[40] For clarification on PMA filing criteria and to better understand the types of information FDA needs to determine if a PMA should be "filed," please see the guidance entitled: "Premarket Approval Application Filing Review," http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM089535.pdf.

[41] For more information on criteria for expedited review, please see the guidance entitled: "Guidance for Industry and FDA Staff: Expedited Review of Premarket Submissions for Devices," http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089698.pdf .

changes. The discussion should describe how this information may have led you to change (i.e., expand, narrow, or re-define) the anticipated patient population, the device design, patient labeling and/or physician/user training (as applicable).

Nonclinical Testing

Your Pre-Sub should provide:

- the list of nonclinical tests conducted in support of your PMA;
- if device design changes have occurred, a master table outlining which test was conducted on each design iteration may be appropriate; and
- your planned format for providing the nonclinical testing information in the PMA.

Clinical Testing

The information about your clinical study should include:

- the patient accountability tree or chart, along with a discussion of how you plan to address missing data in the analysis of your clinical results;
- confirmation that all patients will have reached the primary endpoint evaluation at the time of submission or that the study has otherwise reached the point of completion as defined in the approved protocol, and an explanation of any longer-term follow-up to be submitted in the PMA;
- the proposed format for presentation of clinical study results in the PMA (e.g., tables, charts, summaries, conclusions);
- the proposed indications for use and how your data support each of these indications; and
- any claims you intend to make about your device and the type of data you plan to provide.

Statistical

You should describe any likely deviations from the statistical analysis plan approved in your IDE or established in your investigational plan. You should also identify the statistical program code used to conduct your analyses and in what electronic format you will provide this code and the primary dataset (including an analysis with one line per unit (e.g., person, sample, observation) with the clinical outcomes and baseline covariates).

Labeling

You should provide draft indications for use, contraindications, warnings, and precautions. For an in vitro diagnostic device, you should provide the draft intended use.

Postapproval (Conditions of Approval) Studies

If applicable, you should describe the need for postmarket information, such as continued follow-up of premarket clinical trial cohorts and/or enrollment in a postapproval study (PAS).

Where you have identified the need for a postapproval study, you should discuss your plans in this regard.

3. Examples of Specific Questions for a PMA Pre-Sub

Examples of questions that may be appropriate to consider in a PMA Pre-Sub are given below according to topic.

Clinical

- Is the proposed data format appropriate?
- Is the plan to address any protocol deviations adequate?
- The study did not meet its primary endpoint. Should we proceed and if so, how?

Statistical

- Does FDA have any major concerns regarding the statistical analyses to be submitted?

Postapproval Studies (if applicable)

- What specific information about a postapproval study should the PMA contain?

E. Pre-Sub for an HDE

1. When to Submit a Pre-Sub for an HDE

A Pre-Sub for an HDE should be submitted no less than ninety (90) days prior to submission of the HDE. This will afford time for the agency to provide feedback on the specific questions and for the applicant to modify the planned HDE submission accordingly.

2. Content of Pre-Sub for an HDE

The Pre-Sub should contain sufficient information so that FDA can provide advice on your specific questions. We suggest that you provide the information suggested in Section III. Recommended Information in All Pre-Sub Packages and Section D. Pre-Sub for a PMA, above.

3. Specific Questions for an HDE Pre-Sub

The types of specific questions that you may ask in a Pre-Sub for an HDE are likely to be similar to those that would be asked for a PMA.

Examples of questions that may be appropriate to consider in an HDE Pre-Sub are provided below.

- Does FDA concur with the proposed outline of non-clinical testing?
- Is the proposed clinical analysis plan adequate?

- Is the summarized nature and type of nonclinical and clinical safety information adequate for FDA to begin assessing safety and probable benefit in an HDE (e.g., are data on additional patients likely to be needed)?

F. Pre-Sub for an IVD

1. When to Submit a Pre-Sub for an IVD

The advice FDA provides prior to submission of a marketing application for an IVD may be a highly effective tool in streamlining our review as our advice can aid in identifying planned testing that may be unnecessary or additional testing that we will need to review in the future marketing application. The timing of your Pre-Sub should be reflective of your planning needs, but should allow adequate time for FDA feedback prior to starting any of the studies that are part of the Pre-Sub.

A Pre-Sub should focus on how information will be gathered by the manufacturer to support the intended use and indications for use as proposed. Generally, when preparing a Pre-Sub, a manufacturer should provide a cover letter, intended use statement, device description (including a description of the instruments, reagents, and software), a development history and prior information, designs of proposed studies (including specimen information), analytical plan, clinical plan, statistical analysis plan, administrative information form, related literature, and any specific questions that you want FDA to answer. **If you feel there is something unique or distinct about an aspect of your device or study design, then it may be worthwhile to provide additional detail about your device beyond what is mentioned below.**

2. Content of Pre-Sub for an IVD

- **Elements of Intended Use**

  You should provide a clear statement of the proposed intended use and indications for use. The intended use statement describes how and by whom the device is to be used and should include the following information:

  - Measurand (analyte, biological activity, or some other quantity to be measured) or organism to be identified or detected
  - Whether the test is quantitative, semi-quantitative, and/or qualitative
  - Specimen type(s) or matrix(-ces) (e.g., blood (include source, e.g., venipuncture, heel or finger stick), serum, plasma (include anti-coagulants), stool, hair, swab (include source, e.g., cervical, nasopharyngeal, throat), urine (include time collected), saliva, cerebrospinal fluid (CSF), sweat, tears, etc.)
  - Conditions for use which describes the setting in which the test is to be performed and the intended user (e.g., prescription use (hospital laboratory, point of care, physician's office, home use, workplace) or over-the-counter)

  The indications for use describes for what and for whom the device is to be used (e.g., target condition, target population and purpose). The following are some examples of information included in the indications for use:

- Target condition: a particular disease, disease stage, health status, or any other identifiable condition or event within a patient, or a health condition that should prompt clinical action
- Target patient population , for example:
  - Age (e.g., adult, pediatric, specific age limitations)
  - Asymptomatic patients (e.g., screening)
  - Symptomatic patients (e.g., diagnosis or prediction)
  - Already diagnosed patients (e.g., monitoring or prognosis)
- Time and frequency of use (e.g., glucose testing for stability and rapid changes after meals)
- Purpose for measurement (e.g., clinical indication – how and why the clinician or the user will use the results of the test)

- **Description of How the Device is Planned to be Used in a Real-life Setting**

For novel clinical indications, you should provide a detailed description of how you see your device being used in a real-life setting. You might want to consider diagrams illustrating the clinical management of a hypothetical patient from the proposed target population, including information regarding at what point(s) your device will be used and how information from your device can be used by the user (e.g., physician). It is helpful if you provide a few examples of the use of your device for different patients (with different set of covariates) from the target population.

- **Risk Analysis**

For devices with novel intended uses, you may include an analysis of the impact of false test results on patient management. This information can be useful to aid FDA in determining the appropriate classification of your device. Suggested approaches to mitigate the underlying risks may be presented as part of the risk analysis.

- **Proposed Study Design(s)**

We recommend that you provide a detailed protocol of how you propose to evaluate the analytical and clinical performance characteristics of your device. You may provide descriptions of the studies proposed to support the intended use of your device. In preparation of this section, we recommend that you refer to relevant FDA documents and the standard guidelines, such as the Clinical Laboratory and Standards Institute (CLSI) documents for your device type, as applicable.

- **Specimen Information**

As part of your proposed study design you should indicate the types of specimens that you will recommend for testing. The following may be helpful if you wish to gain advice on specimen use in your studies:

- A description of the sample collection methods recommended and any specific sample collection devices;
- If you propose to utilize more than one sample type, a description of how you propose to evaluate your device performance for the different sample types in your analytical and clinical study designs;
- How you plan to assess sample stability, recommended storage conditions, and parameters to demonstrate the quality and integrity of the samples; and/or
- How you will utilize fresh, frozen, or otherwise preserved samples in the clinical studies.

- **Analytical Performance**

You may submit protocols for analytical validation studies for which you desire FDA feedback. The studies that are necessary to validate the analytical performance of your device may vary depending on the device type (e.g., qualitative, semi-quantitative or quantitative). Many types of analytical performance studies are standardized and follow accepted standard documents such as CLSI documents. It is recommended that you base your studies on such standards, when applicable. The major analytical performance parameters for IVDs may include: accuracy; limit of detection; analytical cut-off of the device; precision (e.g., repeatability, reproducibility); matrix comparison; analytical specificity (cross reactivity and interference); reagent and sample stability studies; reference interval; limit of quantitation; traceability to standard materials; linearity; method comparison; and high dose hook effect.

In any study protocols you propose, we recommend that you indicate for each study: (1) information about the samples used for evaluation and (2) the level of the analyte(s) being measured. You should ensure you clearly describe the proposed study design, the parameters that will be assessed, the acceptance criteria, and the proposed methods for data analysis. If standard guidelines will be followed, we recommend that you specify the guideline used.

- **Method Comparison**

For method comparison study proposals, you should include the proposed study design, comparator (predicate or reference method), and proposed analysis method. Method comparison studies usually compare the device performance to the predicate device. However, for certain device types, the predicate device may not be the appropriate comparator; in some cases, a reference method or clinical diagnosis may be a more appropriate comparator. If there is no predicate device for the device under evaluation, you should propose the appropriate comparator and study design, providing scientific justifications for the proposal(s). The method comparison proposal may include:

- study design,
- study population,
- method for sample size determination,
- study sample size,
- number of testing laboratory sites,
- criteria for sample type selection and justification,
- method of sample collection,
- indication of the number of measurements recorded per individual (as applicable),
- description of comparator or predicate device,
- detailed testing protocols, and
- data analysis protocols (e.g., agreement, regression, and how discrepant or equiv o

You may wish to include any concerns that you have regarding the selection of the predicate or reference method. If you have identified a predicate device, you may also wish to discuss any potential differences from the predicate that may affect the assessment of your device performance.

- **Clinical Performance**

Many IVDs require clinical studies to establish effectiveness. Clinical studies should not be confused with analytical studies that use clinical speci , a study that evaluates test measurement parameters compared to those of another method or device). A clinical study is an evaluation of clinical performance, in which patients are enrolled or specimens are collected in accordance with pre-defined inclusion/exclusion criteria. Clinical performance is often stratified by demographic variables (e.g., age, sex). Performance is generally based on a comparison between the device result and clinical presentation or other marker of disease. In some situations other types of clinical performance evaluation may be considered.

You may submit protocols for clinical performance studies for which you desire FDA feedback. In this section, you should describe studies designed to support your proposed indication(s) for use. Clinical studies often include evaluating parameters such as clinical sensitivity and specificity, positive and negative predictive values, and clinical cut-offs. Other parameters may be addressed as needed.

- **Clinical Study Design Elements**

You should consider including the following in your study design proposal:

- Target condition - brief description of the target condition (diagnosis, stage of illness, signs/symptoms, success of treatment, etc.). Indicate how (criteria, laboratory tests, physical examination) and by whom (i.e., specialist,

generalist) the target condition will be determined. Include demographic information and the prevalence of the target condition.
- Intended use population - description of inclusion/exclusion criteria, and how the clinical study population(s) reflect the intended use population(s).
- Matrix type - listing of the sample matrices to be tested in the clinical study. Sample matrices should be consistent with those claimed in the intended use.
- Sample selection - description of sample types used in the study (e.g., fresh, stabilized, prospective, archived, retrospective, etc.). Describe how samples are selected for inclusion in the studies, how they will be stored, and how their integrity and analyte stability will be assessed. If archived samples are used, consider the potential for bias and describe how it will be addressed.
- Study sites - if known, list potential study sites, and their geographical locations. FDA recommends at least three study sites for your clinical studies. Generally, the device should be evaluated at sites representative of those in which the device ultimately will be used.
- Literature - in some cases, you may be able to use published, peer-reviewed literature to support clinical claims. If you are proposing to use literature to support clinical claims, you should clearly outline your reasons for doing so, and be prepared to discuss your proposal with FDA.

- **Statistical Analysis Plan for Clinical Performance Study**

You should consider including the following, as appropriate:
- Proposed clinical study plan.
- Explanation of sample size that provides a sound statistical basis for the determination of sample size (N).
- Proposed plan for how data will be analyzed (e.g., identify independent and dependent variables, provide interpretation criteria and your definition of positive, negative, or equivocal results).
- Description of how the cut-off or reference range is determined and validated.
- Description of expected results (define or explain calculations; determine equivocal zones and describe if and how discrepant results will be resolved).
- Expected rate of clinical false positives and false negatives, if known.
- Description of the success criteria you will use to determine if your device performs acceptably.