Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff

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Guidance for Industry and Food and Drug Administration Staff

Document issued on: [release date of FR Notice]

This document supersedes Pre-IDE Program: Issues and Answers - Blue Book Memo D99-1, dated March 25, 1999

The draft of this document was issued on: July 13, 2012

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

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

Center for Devices and Radiological Health

Center for Biologics Evaluation and Research

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Preface

Public Comment

You may submit written comments and suggestions at any time for Agency consideration to the Division of Dockets Management, Food and Drug Administration, 5630 Fishers Lane, rm. 1061, (HFA-305), Rockville, MD, 20852. Submit electronic comments to http://www.regulations.gov. Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*. Comments may not be acted upon by the Agency until the document is next revised or updated.

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Additional copies of this guidance document are also available from the Center for Biologics 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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This guidance represents 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

The purpose of this guidance is to provide an overview of the mechanisms available to applicants[1] through which they can request feedback from the Food and Drug Administration (FDA) regarding potential or planned medical device Investigational Device Exemption (IDE) applications or other premarket submissions, such as Premarket Approval (PMA) applications, Humanitarian Device Exemption (HDE) applications, Evaluation of Automatic Class III Designations (de novo petitions), Premarket Notification (510(k)) Submissions, Clinical Laboratory Improvement Amendments (CLIA) Waiver by Application, and including certain Investigational New Drug Applications (INDs) and Biologics License Applications (BLAs). This guidance provides information regarding the logistics for submission, receipt, tracking, and review of/response to these requests.

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

The feedback mechanisms addressed by this guidance include Pre-Submissions, Informational Meetings, Study Risk Determinations, Formal Early Collaboration Meetings (i.e., Agreement and Determination Meetings), Submission Issue Meetings, and PMA Day 100 Meetings. For some of these mechanisms, this document largely refers to existing guidance, while for others, this guidance establishes the procedures FDA intends to follow when providing feedback; however, all of these feedback requests will fall within the same organizational structure for tracking purposes. These requests for feedback will now be collectively referred to as "Q-Submissions" or "Q-Subs." FDA believes that the Q-Sub structure will provide a convenient and effective way to track these requests.

This guidance also provides clear recommendations for applicants regarding the appropriate preparation for, and conduct of, meetings with Center for Devices and Radiological Health (CDRH) and Center for Biologics Evaluation and Research (CBER) staff. However, this guidance does not apply to meeting requests from industry trade organizations, consumer or patient advocacy organizations, other government agencies, or other stakeholders that are not planning a medical device submission to the FDA.

Throughout this guidance document, the terms "we," "us" and "our" refer to FDA staff from CDRH or CBER. "You" and "your" refers to the applicant or sponsor.

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. Background

Since its establishment in 1995, the pre-IDE program has been a successful resource for both medical device applicants and FDA and has become the most commonly used mechanism for requesting FDA's feedback prior to a premarket device submission. Originally, this program was designed to provide applicants a mechanism to obtain FDA feedback on future IDE applications prior to their submission. Over time, the pre-IDE program evolved to include feedback on PMA applications, HDE applications, de novo petitions, and 510(k) Submissions, as well as to address questions related to whether a clinical study requires submission of an IDE. This guidance reflects this broader scope of the program. Accordingly, FDA is changing the name for this program from the pre-IDE program to the Pre-Submission (Pre-Sub) program.[2] This guidance also broadens the scope of the program to include those devices regulated by the Center for Biologics Evaluation and Research (CBER), including those that are regulated as biologics under the Public Health Service (PHS) Act and require submission of an Investigational New Drug Application (IND) and/or a Biologics License Application (BLA).[3]

[2] 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.

[3] This guidance does not provide specific advice or references with respect to Pre-Subs for device INDs or device BLAs submitted to CBER. The sections on Pre-Subs for IDEs and PMAs do provide helpful information.

During the course of developing the Agency's recommendations for the Medical Device User Fee Amendments of 2012 (MDUFA III)[4,5] both industry and the Agency agreed that the Pre-Submission (formerly pre-IDE) process provides important additional transparency to the IDE and premarket review processes. The Secretary's 2012 Commitment Letter to Congress (MDUFA III Commitment Letter)[6] includes FDA's commitment to institute a structured process for managing Pre-Submissions. This guidance establishes such a structured process with clear recommendations for sponsors who submit Pre-Subs, and for FDA staff and managers involved in their review, 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 to the Pre-Sub program, this guidance addresses other types of FDA feedback already available to applicants through other mechanisms. The Food and Drug Administration Modernization Act of 1997 (FDAMA) (Public Law 105-115) established two types of Formal Early Collaboration meetings ("Determination Meetings" as described in section 513(a)(3)(D) of the Food Drug & Cosmetic Act (FD&C Act) and "Agreement Meetings" as described in section 520(g)(7) of the FD&C Act) to provide clear direction for testing and development of devices requiring clinical investigations to support marketing. FDAMA also requires that FDA, upon written request, meet with a PMA applicant no later than 100 days after the receipt of a PMA application that has been filed to discuss the review status of the application (referred to as a "Day-100 Meeting" and described in section 515(d)(3) of the FD&C Act). For other premarket submissions under review, FDA will also grant meetings on an informal basis to discuss our requests for additional information to better ensure that the formal response to FDA's request will fully address the outstanding questions (these meetings are referred to as "Submission Issue Meetings"). FDA will respond to requests for a determination (called "Study Risk Determinations") whether a proposed device study is exempt from or subject to the IDE regulation (21 CFR part 812). For device studies that are subject to the IDE regulations, FDA will also provide its determination whether the study is a significant risk or nonsignificant risk study in response to a voluntary request for this information. In some cases, sponsors may wish to inform or educate FDA about ongoing device development or planned submissions without a

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However, you should contact the Regulatory Project Manager (RPM) in the CBER product office that is responsible for the review of the product for additional guidance, if needed.

[4] See Title II of the Food and Drug Administration Safety and Innovation Act (FDASIA) (P.L. 112-144), amending sections 737, 738, and 738A of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

[5] Meeting minutes from discussions with the medical device industry on the development of the Agency's recommendations for MDUFA III are available at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/MedicalDeviceUserFeeandModernizationActMDUFMA/ucm236902.htm.

[6] MDUFA III Commitment Letter, available at http://www.fda.gov/downloads/MedicalDevices/NewsEvents/WorkshopsConferences/UCM295454.pdf (this document is dated April 18, 2012; it has not changed since then).

specific request for feedback. FDA will, as resources allow, grant requests for such "Informational Meetings." This guidance establishes a structured process for obtaining the types of feedback described in this paragraph.

FDA provides advice to industry during the developmental stage of IDE, 510(k), PMA, HDE, IND and BLA submissions in a number of ways. In addition to the Pre-Sub program and the mechanisms described above, there are several other means by which industry may obtain feedback from FDA, including the CDRH Device Advice website,[7] CDRH's Division of Small Manufacturers, International and Consumer Assistance (DSMICA),[8] CBER's Manufacturers Assistance and Technical Training Branch,[9] and relevant guidance documents. These mechanisms, as well as 510(k) summaries, decision summaries, or summaries of safety and effectiveness (SSEDs) for similar legally marketed devices, may be helpful resources, and are available on our websites.[10] We strongly recommend that you make use of our online information and other available resources prior to submitting any request for feedback.

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, as the preferred method of feedback in response to a Pre-Sub, as an early collaboration meeting, or to discuss an existing regulatory submission. This guidance also provides recommendations regarding how to prepare for meetings with FDA staff. Note that this guidance does not address FDA's formal communications with sponsors or the use of interactive review during the active review of a premarket submission. Please see the draft guidance "Types of Communication During the Review of Medical Device Submissions," (http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm341918.htm). FDA's draft guidance represents FDA's proposed approach on this topic. The guidance also does not address Appeal meetings, which are described in "Center for Devices and Radiological Health Appeals Processes - Guidance for Industry and Food and Drug Administration staff" (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm284651.htm), or for submissions made to CBER, "Guidance for Industry: Formal Dispute Resolution: Appeals Above the Division Level" (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079743.pdf) and CBER SOPP 8005: Major Dispute Resolution Process (http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm109574.htm) .

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

[8] You may contact DSMICA by email at dsmica@fda.hhs.gov or industry.devices@fda.hhs.gov; or by telephone: 1-800-638-2041 or 301-796-7100.

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

[10] 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

III. Requests for FDA Feedback

As stated in the introduction, this guidance provides information regarding existing mechanisms for requesting FDA feedback, and also establishes several new mechanisms, all of which will now fall within the same organizational "Q-Sub" structure for tracking purposes. The various types of Q-Subs addressed in this guidance and the timeframes within which FDA intends to provide the requested feedback are described in Table 1 below.

Table 1

Q-Sub Type	Meeting as Method of Feedback?	Timeframe for Meeting/Teleconference (from receipt of submission)
Pre-Submission*	Upon request	75-90 days**
Informational Meeting	Yes	90 days
Study Risk Determination	No	N/A
Agreement Meeting	Yes	30 days or within time frame agreed to with sponsor
Determination Meeting	Yes	Date for meeting agreed upon within 30 days of request
Submission Issue Meeting	Yes	21 days
Day 100 Meeting	Yes	100 days (from PMA filing date)

*As defined in MDUFA III Commitment Letter.
**21 days for urgent public health issues (see Section III.A.6.).

FDA intends to assign a unique identification number to all Q-Subs, using a similar format to other premarket submissions. These requests will be assigned a number starting with "Q,"[11] followed by two digits representing the year, and four digits representing the order in which the request was received during that calendar year. Therefore, the first such submission received in January of 2014 will be identified as "Q140001." A supplement submitted for this request will be identified as "Q140001/S001." As with IDE submissions, FDA will keep the existence of these "Q-Subs" confidential,[12] subject to the confidentiality provisions of the FD&C Act, FDA's Part 20 regulations covering information disclosure, and the Freedom of Information Act (FOIA) (5 U.S.C. § 552).

Submitting a Q-Sub

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

To expedite processing of your Q-Sub, we recommend that the first paragraph of your cover letter and/or the CDRH Premarket Review Submission Cover Sheet,[13] if used, identify the Q-Sub type from Table 1 above and the preferred method of feedback (written, teleconference, or meeting).

You must submit an eCopy (section 745(A)(b) of the FD&C Act). For information about how to comply with the eCopy program, please see FDA guidance "eCopy Program for Medical Device Submissions"

[11] Q-Subs submitted to CBER will be assigned a number starting with "BQ"
[12] Refer to 21 CFR 812.38.
[13] CDRH Premarket Review Submission Cover Sheet available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM080872.pdf

(http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM313794.pdf). Q-Subs for products regulated by CDRH should be sent to:

U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Control Center – WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Q-Subs for products regulated in the Center for Biologics Evaluation and Research (CBER) should be sent to the address below.

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

For submissions to CDRH, on the business day that the Q-Sub is received by the Document Control Center (DCC), the Q-Sub is assigned a unique tracking identifier by the DCC as described above. Any future communications regarding your Q-Sub should include this unique Q-Sub identifier. The Q-Sub contact will be mailed an acknowledgement letter that contains the unique tracking number and date received by the DCC. 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 Received Prior to Submitting Investigational or Marketing Applications (Pre-Application) (http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm079476.htm). After the CBER DCC processes your Device Q-Sub, it will be forwarded to the appropriate Product Office for additional processing and review. You will be contacted by the Regulatory Project Manager (RPM) who will provide you with a BQ number and who will be your contact for all additional communications.

Acceptance Review

Within 14 calendar days of receipt of a Q-Sub that includes a valid eCopy, FDA staff will conduct an acceptance review using the Acceptance Checklist (see Appendix 2) to (1) determine if the request meets the definition of the identified Q-Sub type and (2) determine if a qualifying request is administratively complete.

The staff should first assess whether the submission meets the definition of the interaction type identified by the applicant by answering questions 1 and 2 in the Acceptance Checklist. If the submission meets the definition of a Pre-Submission, an Informational Meeting request, or a

Submission Issue Meeting request, staff should then apply the applicable section of the Acceptance Checklist to ensure the submission is administratively complete.

If the submission does not meet the definition of the Q-sub type identified by the applicant, but appears to meet the definition of another type of meeting request (e.g., the Q-Sub is identified as an Informational Meeting request, but appears to meet the definition of a Pre-Sub), staff should apply the appropriate section of the Checklist and if the submission is complete, accept the submission and proceed according to the appropriate corresponding timelines. If the Q-sub appears to be a request for an Early Collaboration Meeting (Agreement or Determination meeting), PMA Day 100 Meeting, or a Study Risk Determination, staff should accept the Q-sub and proceed with review and feedback as described in applicable existing guidance documents or SOPs. If the submission does not include sufficient information for FDA to determine what type of feedback is being sought by the applicant, the staff should obtain concurrence of the branch chief, designate the submission as refuse to accept (RTA), and notify the applicant in writing that the submission has not been accepted and the reasons for not accepting it.

Once the applicant has responded to the RTA with sufficient information such that the submission can be determined to meet the definition of a Pre-Sub, an Informational Meeting request, or a Submission Issue Meeting request, the staff should complete the applicable section of the Acceptance Checklist. Unlike the acceptance reviews for 510(k) and PMA submissions,[14] this acceptance checklist does not include a list of required elements, where each element must be present for the submission to be accepted. Instead, the Acceptance Checklist is intended to ensure only that the submission includes sufficient information for FDA to provide the requested feedback and/or identify the appropriate FDA attendees so that the meeting or teleconference can be scheduled. If this basic information is present, but some additional clarifying or explanatory information is needed, the Q-Sub should be accepted and the lead reviewer[15] should contact the applicant to obtain the additional information. If the Pre-Sub, Informational Meeting request, or Submission Issue Meeting request does not contain this information, staff should obtain branch chief concurrence, designate the Q-Sub as refuse to accept (RTA), and notify the applicant in writing that the submission has not been accepted and the reasons for not accepting it.

The applicant may respond to the RTA notification by providing additional information, which will be logged in as an amendment to the Q-Sub. Upon receipt of the newly submitted information, FDA staff should conduct the acceptance review again following the same procedure within 14 calendar days of receipt of the new information. The subsequent acceptance review will assess whether the new information makes the submission complete according to the checklist criteria for completeness. If the submission is still found to be incomplete, FDA staff should notify the contact person.

[14] See FDA's guidance documents "Refuse to Accept Policy for 510(k)s" (http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM315014.pdf) and "Acceptance and Filing Reviews for Premarket Approval Applications (PMAs)" (http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM313368.pdf).

[15] In the case of Q-Subs sent to CBER, the RPM will manage the interactions with the applicant.

Once the Q-Sub has been accepted, if a meeting or teleconference has been requested, the lead reviewer should contact the applicant within 7 days of the acceptance to propose one or more potential meeting dates and times.

A. The Pre-Sub Program

A Pre-Submission is defined as a formal written request from an applicant/sponsor 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 main purpose of the Pre-Sub program remains the same as the previously established pre-IDE program: to provide the opportunity for a sponsor to obtain FDA feedback prior to an intended submission of an IDE or marketing application. The Pre-Sub program can also provide a mechanism for the Agency to provide advice to sponsors who are developing protocols for clinical studies for which an IDE would not be required, such as studies of non-significant risk (NSR)[16] 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.

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 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 in situations when specific questions arise which are not adequately addressed by existing guidance. It is the applicant's decision whether or not to submit a Pre-Sub prior to submission of an IDE, 510(k), PMA, HDE, (CLIA) Waiver by Application,[17] IND or BLA. 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.

FDA recognizes that there may be circumstances in which a manufacturer of a combination product[18] or device constituent part of a combination product would like to interact directly with CDRH regarding the device constituent part through the Pre-Submission process even if another center (i.e., the Center for Drug Evaluation and Research (CDER) or the Center for Biologics Evaluation and Research (CBER)) may be designated as the lead center for premarket review of the combination product. CDRH believes that it may be appropriate to submit a Pre-Sub in

[16] Please see 21 CFR 812.3(m) (definition of significant risk device) and the guidance "Significant Risk and Nonsignificant Risk Medical Device Studies," (http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126418.pdf). .

[17] For more information, see "Recommendations: Clinical Laboratory Improvement Amendments of 1988 (CLIA) Waiver Applications for Manufacturers of In Vitro Diagnostic Devices," (http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm079632.htm).

[18] As defined in 21 CFR 3.2(e).

situations where the manufacturer is seeking input regarding the device constituent part only and there is not expected to be any impact on the other constituent part of the combination product. For example, a sponsor is requesting feedback on the proposed mechanical testing for a new infusion pump. Such testing would be applicable to the pump regardless of the drug or biological product being delivered by the pump. If such a Pre-Sub is submitted to CDRH, it is recommended that CDRH staff notify the lead center for the combination product of the receipt of the Pre-Sub and involve the appropriate review staff from the other center(s) to ensure the entire combination product review team is aware of the questions from the sponsor and the feedback provided. In situations where sponsors request participation of staff from both centers involved with the review of the combination product, the request should be submitted to the lead center in accordance with that center's pre-submission process. Please note that meetings or requests for written feedback that involve participants from two or more centers may take longer to schedule and/or to address in writing, due to the increased number of participants, the need to consider two or more regulatory paradigms, and the added complexity that exists for many combination products.

1. When to Submit a Pre-Sub

Pre-Subs are generally useful for early feedback on specific questions during submission preparation, such as in the following circumstances:

a. Before conducting clinical, nonclinical, or analytical studies, or submitting an IDE, IND, 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;
- you are proposing a "first of a kind" indication or a new indication for an existing device;
- the new device does not clearly fall within an established regulatory pathway, and you desire informal input on a proposed regulatory strategy;
- 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[19] of or the reference method is unclear or uncertain;
- you desire FDA guidance on specific issues related to nonclinical study protocols and/or animal study protocols, 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, such as when there is no recognized consensus standard or are multiple standards from which to choose;

[19] FDA recognizes that sponsors may cite more than one predicate to support a finding of substantial equivalence within a 510(k) submission. "Predicate" and "predicates" are used interchangeably in this guidance.

- 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 or IND, such as for a nonsignificant risk device or a study you plan to conduct entirely outside the US (OUS).

b. 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 or IND);
- to obtain feedback on the use of data collected from an OUS study to support clearance or approval;
- 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), some of which could require additional data or analyses.

FDA encourages sponsors to review all relevant cross-cutting and device-specific guidances prior to preparing a Pre-Submission.

2. Using the Pre-Sub Program

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, FDA will track all subsequent requests for feedback that also meet the definition of a Pre-Sub as supplements to the original Pre-Sub. In general, a Pre-Sub should include requests for feedback related to: a specific device/indication combination, a set of one or more devices/products intended to be used or marketed together, or a device "platform" upon which multiple devices will be built. FDA will track additional information (such as presentation slides), meeting minutes, and requests for clarification as amendments to the initial request for feedback, whether in an original Pre-Sub or in a Pre-Sub supplement. Requests for additional feedback following an initial Pre-Sub interaction, such as review of a revised protocol following the initial meeting, should be submitted as a Pre-Sub supplement. However, the number of Pre-Subs and Pre-Sub supplements submitted should be carefully considered to avoid confusion and unnecessary expenditure of both FDA and industry time and resources.

FDA will include appropriate expertise on the review team for a Pre-Sub; however, 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 generally not appropriate for the Pre-Sub program. However, if the data and conclusions are difficult to interpret, it may be appropriate to ask a specific question regarding

the interpretation of preliminary results or the planned approach for addressing the results within the upcoming submission.

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 topics associated with the Pre-Sub under review, 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. For example, it may be appropriate to request a Pre-Sub to discuss the pre-clinical testing for your device and subsequently submit a Pre-Sub supplement to discuss a clinical study protocol. 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, IND, 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 address the issues and recommendations provided 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 when all information is reviewed and considered as a whole. 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 (see Section III.A.4.).

3. 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 such as those described in other sections of this guidance and detailed below. 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 III.B Informational Meetings below);

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

  Although most requests for clarification are not appropriate for a Pre-Sub, 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 by a guidance document;
  - recommendations for nonclinical or clinical studies not addressed by a 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 review staff (examples of these types of questions include technical questions such as whether FDA routinely accepts a particular test method for a nonclinical test, or whether a particular standard is applicable to the applicant's device; as well as procedural questions such as how long the applicant has to respond to a request for additional information, or where to find publicly available information about potential predicate devices); or

- meetings or teleconferences requested by either the applicant or FDA to discuss FDA requests for additional information for a marketing application under review or on hold (See Section III.E Submission Issue Meetings).

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, HDE, IND or BLA has been submitted. (For more information, please see the draft guidance, "Types of Communication During the Review of Medical Device Submissions," (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm341918.htm). FDA's draft guidance represents FDA's proposed approach on this topic.);

- 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 (http://www.fda.gov/CombinationProducts/default.htm) 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 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 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 guidance entitled, "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);

- a mechanism to appeal a decision on a premarket submission (To provide information on appealing a decision, FDA has issued a guidance entitled, "Center for Devices and Radiological Health Appeals Processes," (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm284651.htm), or for submissions made to CBER, see "Guidance for Industry: Formal Dispute Resolution: Appeals Above the Division Level" (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079743.pdf) and CBER SOPP 8005: Major Dispute Resolution Process (http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm109574.htm));

- a request for Evaluation of Automatic Class III Designation (de novo) classification or related inquiries (For information on the de novo process, see the draft guidance entitled, "De Novo Classification Process (Evaluation of Automatic Class III Designation)" (http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm273902.htm). FDA's draft guidance represents FDA's proposed approach on this topic.); or

- a determination meeting under Section 513(a)(3)(D) of the FD&C 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 (see Section III.D. below).

4. Pre-Sub Feedback

FDA feedback to a Pre-Sub can be provided in multiple ways, including through an in-person meeting, a teleconference, facsimile,[20] or by email.[21] If FDA feedback will be through a meeting or teleconference, at least 3 business days[22] 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. Otherwise, the meeting minutes will be considered FDA's final written feedback. FDA will aim to provide complete feedback to a Pre-Sub, either in writing or as part of a meeting/teleconference within 75 days, but no later than 90 days after receipt of a complete package (see Section III.A.6 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. 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. For example, FDA may modify our previous feedback if new scientific findings emerge that indicate there is a new risk or an increased frequency of a known risk that affects our prior advice; or if there is a new public health concern that affects our prior advice. 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.[23] Further, FDA intends to work with the

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

[21] 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.

[22] While this "3-day" feedback is based on business days, all other references to "days" in this guidance mean calendar days.

[23] 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

sponsor to address any new issues raised by the change, taking into consideration the stage of device development, where possible.

Because clinical practice is constantly evolving, 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 our previous advice is still valid. This can be accomplished through a phone call to the lead reviewer or branch chief; a new Pre-Sub is not needed.

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 Appendix 1: Recommendations for Specific Types of Pre-Subs.

5. Recommended Information for Pre-Sub Packages

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. If you plan to conduct a study OUS to support a marketing application, we recommend discussing the full protocol through the Pre-Sub process prior to initiating the study.

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, Pre-Sub for an IND or BLA) and, for CDRH submissions, please clearly indicate that the submission is a Pre-Sub on the CDRH Premarket Review Submission Cover Sheet.[24] 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

[24] CDRH Premarket Review Submission Cover Sheet available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM080872.pdf

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, where appropriate, between sections, and sequential numbering of the pages of your hard copy Pre-Sub package. Electronic copies should follow the formatting requirements as outlined in the eCopy guidance referenced in Section III. "Submitting a Q-Sub" above.

c. Device Description

Please provide sufficient information regarding the device description,[25] 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);
- 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 descriptive comparison of the device to the predicate 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.[26]

[25] 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.
[26] If you wish to submit a video, you must include that as part of your eCopy.

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 1 for more detailed information).

e. Previous Discussions or Submissions

Please summarize any previous discussions with/submissions to (including submission numbers) the agency on this or a similar device (e.g., previous discussions on a prior device design), including submission numbers as appropriate.

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 include a review of 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. Appendix 1 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. Method 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 method requested in the Pre-Sub. If FDA has already agreed to a meeting,

it is the sponsor's decision regarding whether this previously scheduled meeting should occur even if FDA has provided a written response to the sponsor's questions. If we provide feedback through a meeting or teleconference, the final meeting minutes will be considered FDA's formal written feedback (see Section IV.D. below).

If you are requesting a meeting or teleconference as the method for feedback, your submission 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 in Table 1 above for scheduling;
- 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 IV. B. "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.

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.

6. Scheduling Pre-Sub Meetings and Teleconferences

If an accepted Pre-Sub requests a meeting or teleconference, FDA will review the information, determine if the request necessitates more than one meeting or teleconference, and work with the applicant to set a mutually agreeable time and date for the meeting or teleconference.

FDA will aim to schedule a Pre-Sub Meeting within 75 days, but no later than 90 days after 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, or sooner if possible. 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 at least 14 days prior to the urgent meeting to ensure that FDA staff have adequate time for review. If the information is not received 14 days prior to your meeting date, we may contact you to reschedule the meeting for a later date.

B. 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.

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

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.

1. Recommended Information for an Informational Meeting Request

We recommend your Informational Meeting request include the information below:

- a cover letter that clearly identifies the submission type in the reference line (i.e., Informational Meeting request) and, for CDRH submissions, please clearly indicate that the submission is an Informational Meeting request on the CDRH Premarket Review Submission Cover Sheet. Use of the CDRH Premarket Review Submission Cover Sheet for submissions made to CBER is highly recommended;
- a brief statement describing the purpose, scope, or objectives of the meeting;
- a proposed agenda describing the devices and/or topics to be presented and the estimated time for each agenda item;
- 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 given the guidelines in Table 1 above for scheduling;
- 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 IV.B. "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.

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.

2. Scheduling Informational Meetings and Teleconferences

FDA will aim to schedule an Informational Meeting or Teleconference within 90 days of receiving the meeting request.

C. Study Risk Determinations

The IDE regulations (21 CFR part 812) describe three types of device studies: significant risk (SR), nonsignificant risk (NSR), and exempt studies. For studies that are not exempt, sponsors are responsible for making the initial risk determination (SR or NSR) and presenting it to the Institutional Review Board (IRB). For more information, please see Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors Significant Risk and Nonsignificant Risk Medical Device Studies (http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126418.pdf). FDA is available to help the sponsor, clinical investigator, and IRB in making the risk determination. FDA will review written requests from sponsors planning a device clinical study and provide our risk determination in writing. Note that FDA is the final arbiter as to whether a device study is SR or NSR and makes the determination when an IDE is submitted to FDA or if asked by the sponsor, clinical investigator, or IRB. See 21 CFR 812.2(b)(1).

1. Recommended Information for a Study Risk Determination Request

Please clearly indicate in your cover letter that the submission is a "Study Risk Determination" in the reference line. A request for a study risk determination should also include the following information:

- a cover letter that clearly identifies the submission type in the reference line (i.e., a Study Risk Determination request) and, for CDRH submissions, please clearly indicate that the submission is an Study Risk Determination request on the CDRH Premarket Review Submission Cover Sheet. Use of the CDRH Premarket Review Submission Cover Sheet for submissions made to CBER is highly recommended;
- a detailed device description (for each device, if more than one is in the study);
- the protocol for the study;
- a description of how the device will be used, if not included in the protocol;
- a description of the population, if not included in the protocol; and
- the sponsor's name and contact person(s), including titles, address, phone number, fax number, and email address.

2. Procedures for Study Risk Determination Requests

You should submit your Study Risk Determination request to the appropriate address as outlined in Section III. "Submitting a Q-Sub" above and FDA will assign the submission a Q-Sub

number. Submission of a study risk determination request does not obligate the sponsor to submit an IDE, nor is there a user fee for the request. FDA will send the sponsor an acknowledgement letter indicating the Q-Sub number assigned; you should use this number for all future communications regarding that submission.

Once a determination is made, FDA will issue a letter to the sponsor indicating whether the study is exempt, or, if not exempt, is considered SR or NSR. The letter may be copied and submitted to IRB(s) with the protocol. Once FDA has made a determination, the IRB does not need to conduct an independent assessment of risk; FDA's determination is final.

D. Formal Early Collaboration Meetings

The FD&C Act, as amended by FDAMA, provides for two early collaboration meetings; Determination Meetings and Agreement Meetings. These meetings are intended to facilitate interaction between FDA and applicants and provide clear direction for testing and development of those devices requiring clinical investigations to support marketing. Summary information about these meetings is provided below; for more specific information regarding requests for early collaboration meetings, including the contents of a meeting request and associated meeting activities, see the FDA guidance, "Early Collaboration Meetings Under the FDA Modernization Act (FDAMA)" (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073604.htm).

A Determination Meeting, as described in section 513(a)(3)(D) of the FD&C Act, is available to anyone anticipating submitting a PMA or product development protocol (PDP) and is intended to provide the applicant with the Agency's determination of the type of valid scientific evidence that will be necessary to demonstrate that the device is effective for its intended use. As a result of this meeting, FDA will determine whether clinical studies are needed to establish effectiveness and, in consultation with the applicant, determine the least burdensome way of evaluating device effectiveness that has a reasonable likelihood of success.

The other type of early collaboration meeting is an Agreement Meeting, described in section 520(g)(7) of the FD&C Act, which is open to any person planning to investigate the safety or effectiveness of a class III device or any implant, including submitters of 510(k)s for eligible devices. The purpose of this meeting is to reach agreement on the key parameters of the investigational plan (see 21 CFR 812.25), including the clinical protocol.

The FD&C Act makes it clear that the determinations or agreements resulting from these meetings are to be binding. In the case of a Determination Meeting, the determination regarding valid scientific evidence is binding on the Agency and cannot be changed unless FDA concludes that adhering to it could be contrary to public health. In deciding what type of clinical studies should be conducted, if any, the Agency is charged with considering, in consultation with the applicant, the least burdensome way of evaluating device effectiveness that has a reasonable likelihood of success. In the case of an Agreement Meeting, the agreement is binding on the Agency. The statute specifies that the Agency may only change the agreement when a substantial scientific issue essential to determining the safety or effectiveness of the device has

been identified, and only following an opportunity for the applicant to meet with FDA to discuss the scientific issue involved.

The binding nature of the agreement or determination is predicated on the applicant not significantly changing the bases of the agreement or determination (e.g., intended use and indications, product design, investigational plan, clinical study protocol, etc.). If these bases are significantly changed, then the agreement or determination will have been abrogated and the Agency's agreement or determination will no longer be in effect.

E. 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, PMA, IND or BLA application or CLIA Waiver by Application, including associated amendments or supplements, 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 intended to provide clarification of FDA's questions and/or to discuss an approach to responding to complex issues.[27] Submission of a Q-Sub for a Submission Issue Meeting is appropriate when:

- the sponsor requests an in-person meeting to discuss their planned approach to responding to deficiencies;
- the sponsor requests a teleconference with management participation to discuss their planned approach to responding to deficiencies; or
- the sponsor requests feedback that requires in-depth preparation by the review team and management due to the nature of the questions. For example, if a sponsor requests feedback on plans to submit a justification for not providing the information requested in one or more deficiencies, FDA will likely recommend submission of a Q-Sub, as this type of question typically requires input from FDA management.

A Q-sub for a Submission Issue Meeting is not generally needed for brief clarification questions that can be readily addressed by the lead reviewer, or for teleconferences for which the sponsor has not requested the participation of a manager. Such discussions should be documented in the review record associated with the parent submission.

If a sponsor desires FDA feedback on a proposed protocol prior to conducting a major (clinical or animal) study to address a deficiency, a Submission Issue Meeting is usually not the appropriate mechanism. To allow the review team adequate time to review the proposed protocol, the sponsor should instead submit the protocol and focused questions for FDA feedback in a Pre-Submission (See Section III.A).

Note that a Submission Issue Meeting is not appropriate for:

- a pre-review of planned responses. This information should be reviewed only within a formal response to the deficiency letter, submitted to the DCC; or

[27] 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.

- interactive review (for more information on use of interactive review, please see the draft guidance "Types of Communication During the Review of Medical Device Submissions," (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm341918.htm) which, when final, will represent the Agency's thinking on this topic.)

Day 100 meetings for original PMAs and Panel-track PMA Supplements are a subset of Submission Issue Meetings and are addressed specifically in Section III.E.3 below.

1. Recommended Information for a Submission Issue Meeting Request

In general, 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, tracked with a Q number, and linked to the submission under review through our electronic tracking system and in the lead reviewer's memoranda. We recommend your Submission Issue Meeting request include the information below:

- a cover letter that clearly identifies the submission type in the reference line (i.e., Submission Issue Meeting request) and, for CDRH submissions, please clearly indicate that the submission is a Submission Issue Meeting request on the CDRH Premarket Review Submission Cover Sheet. Use of the CDRH Premarket Review Submission Cover Sheet for submissions made to CBER is highly recommended;
- a reference to the premarket submission number and any other related documents;
- a brief statement describing the purpose, scope, or objectives of the meeting;
- a proposed agenda describing the deficiencies for discussion and the estimated time for each agenda item;
- focused questions for which you are seeking guidance from FDA, if applicable;
- 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 given the guidelines in Table 1 above for scheduling;
- 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 IV.B. "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.

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.

2. Scheduling Submission Issue Meetings and Teleconferences

FDA will aim to schedule Submission Issue Meetings within 21 days of the receipt of the meeting request.

3. Day 100 Meetings for PMA Applications

A PMA applicant may request a Day 100 Meeting to discuss the review status of their PMA application. As outlined in FDAMA, FDA will meet with an applicant no later than 100 days after the receipt of a PMA application that has been filed. Prior to the meeting, FDA is to inform the applicant in writing of any identified deficiencies based on an interim review of the entire application and what information is required to correct those deficiencies.

FDA recommends that a request for a Day 100 Meeting be submitted with the original PMA or as a Q-Sub (Day 100 Meeting Request) no later than 70 days from the PMA filing date so that FDA has sufficient time to schedule the meeting. If the request is made within the original PMA, the PMA Staff will have the request logged in as a Q-Sub and assigned to the appropriate review division. In the request, the applicant should specify the type of meeting desired (e.g., in-person, teleconference) and identify several possible dates for the meeting.

If the request is made after the PMA has been submitted, a written request, identified as a "Submission Issue Meeting request – Day 100 Meeting" should be submitted to the appropriate Document Control Center address in Section III "Submitting a Q-Sub" above. This request will be logged in as a Q-Sub and tracked as a sub-type of a Submission Issue Meeting request. In the written request, the applicant should specify the type of meeting desired (e.g., in-person, teleconference), provide a list of the persons who will attend on behalf of the applicant, and identify several possible dates for the meeting. Applicants may choose to submit additional background information or other meeting materials prior to a Day 100 Meeting, but such information is not required. Given that the focus of a Day 100 meeting is pre-defined, an acceptance review is not necessary.

After a letter filing the application has been issued, the reviewing division will contact the applicant to set up the meeting if requested. As provided by the statute, FDA and the applicant may, by mutual consent, establish a different time for the Day 100 Meeting. FDA will communicate the identified deficiencies to the applicant as part of the Substantive Interaction[28] within 90 days from the filing date of the PMA or 10 days prior to any Day 100 Meeting, if the applicant and FDA agree on a different meeting timeframe.

[28] Substantive interactions are defined in the MDUFA III Commitment Letter, available at http://www.fda.gov/downloads/MedicalDevices/NewsEvents/WorkshopsConferences/UCM295454.pdf (this document is dated April 18, 2012; it has not changed since then). See also the draft guidance "Types of Communication During the Review of Medical Device Submissions" (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm341918.htm). FDA's draft guidance represents FDA's proposed approach to this issue.

The PMA review team as well as the branch chief and division management will attend the meeting with the applicant. Other attendees may be invited as appropriate (e.g., Program Operations Staff (POS)). During the meeting the following may occur:

- a general discussion of identified issues and discussion of remedial actions,
- a discussion of an action plan with estimated dates of completion,
- a discussion of FDA estimated timetables for review completion,
- identification of the need for panel involvement,
- a discussion of possible premarket versus postmarket requirements.

Please refer to FDA's Guidance on PMA Interactive Procedures for Day-100 Meetings and Subsequent Deficiencies - for Use by CDRH and Industry (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080190.htm) for additional information regarding Day 100 Meetings.

IV. Meetings with CDRH and CBER Staff

The meetings with industry and other sponsors described above allow for an open discussion and exchange of technical, scientific, and regulatory information. These meetings can help build a common understanding of FDA's views on clinical, nonclinical, or analytical studies related to an IDE or marketing application.

Meeting requesters should be aware that all meetings are subject to disclosure review pursuant to the Freedom of Information Act (FOIA). Meeting minutes and materials, like all agency records, may be the subject of a FOIA request and unless the information being requested is classified as commercially confidential or trade secret, it will be released to requesters.

A. FDA Response to Meeting Requests

After acceptance and review of 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 within 14 days of receipt of your submission.

1. Scheduling the Meeting

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 the meeting request is accepted as described in Section III above, 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.

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 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. If you believe that information you are submitting is exempt from disclosure, you may mark the slide "confidential." However, this notation will not determine whether the

document is releasable. It is FDA's responsibility to determine what is releasable under FOIA.[29] You should provide the slides 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. We encourage you to bring at least one hard copy of your slides to the meeting in case of an equipment failure. FDA acknowledges that after reviewing FDA's initial feedback, you may wish to make minor modifications to the slides or choose to limit the meeting presentation to a subset of the initial slides in order to focus on relevant items for discussion. 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, inclusion of significant modifications or additional information in the presentation slides may result in the need to reschedule the meeting.

B. 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. The FDA point of contact will meet you at security approximately 10 minutes in advance of your meeting to escort you to the room to set up.

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[30] 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.

[29] See 21 CFR 20.27.

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

C. 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.[31]

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 needs adequate time to thoroughly review, comment on, and 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.

D. Activities after the Meeting

If requested, FDA will provide you a copy of the attendance sign-in sheet at the end of the meeting or will follow-up with an email listing the names of all FDA participants.

[31] 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.

Following the meeting or teleconference, you should develop draft minutes and provide the draft minutes as an amendment to the Q-Sub through the appropriate DCC within 15 calendar days of the meeting. If slides were presented, the actual version used in the meeting or teleconference should be included with the draft minutes in the amendment. Submission of the meeting minutes as a formal amendment is intended to ensure that the receipt date for the minutes and FDA's review of the minutes are tracked appropriately. Rather than being a transcript 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. If FDA does not have any edits to the draft minutes, the minutes will be considered final and FDA will communicate our acceptance of the minutes via email. 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 FDA that there is a disagreement with how a significant issue or action item has been documented. If such a disagreement exists, you should submit an amendment to the Q-Sub through the appropriate DCC, labeled as a "meeting minutes disagreement." In the case of a disagreement, 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 should 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.

E. 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, you and the agency will have to expend additional resources developing and assessing alternative approaches.

Appendix 1
Recommendations for Specific Types of Pre-Subs[32]

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,[33] but must meet all other requirements of 21 CFR 812.119 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" (http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071230.pdf).

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.

[32] Appendix 1 does not provide specific advice with respect to Pre-Subs for device INDs or device BLAs submitted to CBER. The sections on Pre-Subs for IDEs and PMAs provide helpful information. However, you should contact the RPM in the CBER product office that is responsible for the review of the product for additional guidance.

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

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 initiating 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.A.5 "Recommended Information for Pre-Sub Packages," please consider whether the information below will be useful for providing advice on your IDE.

Planned Nonclinical Testing

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 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. For such studies, it may be appropriate to submit the entire study protocol in the Pre-Sub. Refer to Section F of this Appendix 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 in Section A.2 "Content of Pre-Sub for an SR Device Study Requiring an IDE Application."

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. of this Appendix, "Examples of Specific Questions for an IDE Pre-Sub."

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 III.A.3 of this guidance, 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 513(g) program or contact with the Office of Combination Products.[34]

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.A.5 of this guidance, "Recommended Information for Pre-Sub Packages," we suggest that you also provide the following, where applicable.

Proposed Predicate Devices

The 510(k) review process focuses on the comparison of a proposed device with a predicate device in terms of intended 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 intended use, indication(s) for use and technological characteristics of the device you would like to market.

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;[35] and
- a comparison with the proposed device in terms of indications for use, technological characteristics, and performance testing.

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

[34] 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.

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

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. FDA will only make this comprehensive evaluation during its 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?
- Does the FDA concur with the use of the proposed alternative test method, which is different than the normally recognized standard?
- 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?[36]

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 the agency has been able to complete a review of the nonclinical testing.)
- If clinical data are needed for my device, are the proposed trial design and selected control group appropriate or is the protocol from a previously conducted study appropriate?

Predicate Device

- Are there concerns with the predicate device proposed?

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

- Will the information outlined in my Pre-Sub support a substantial equivalence determination?
- Are the results of my bench testing acceptable?
- Is the clinical data collected sufficient?

[36] 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.

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 to any device-specific discussions. You should submit a Pre-Sub for a PMA 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 you to modify the planned PMA submission accordingly.

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.A.5 "Recommended Information for Pre-Sub Packages," 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;[37]
- 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 (if known);
- a discussion of any issues raised in a previous Pre-Sub and confirmation that those issues have been addressed and if any alternative means are utilized, a brief discussion of those means;
- a discussion of your rationale for qualification for priority review, if you plan to request priority status in your submission;[38]

[37] 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: "Acceptance and Filing Reviews for Premarket Approval Applications (PMAs)," http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM313368.pdf.

[38] For more information on criteria for priority review, please see the guidance entitled: "Priority Review of Premarket Submissions for Devices," http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089698.pdf.

- 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 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 intended use, contraindications, warnings, and precautions.

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

You should submit a Pre-Sub for an HDE 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 you 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.A.5 of this guidance, "Recommended Information for Pre-Sub Packages" and Section D. of Appendix 1, "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 described in the Pre-Sub.

2. Content of Pre-Sub for an IVD

A Pre-Sub should focus on how you will gather information to support the intended use and indications for use as proposed. Generally, when preparing a Pre-Sub, you should provide a cover letter, intended use statement, device description (including a description of the instruments, reagents, and software), discussion of relevant 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 believe 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.

- **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; donor or patient), 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.) and any processing required

- 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, blood donor facility, 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)
  - Recipient of blood or tissue products (e.g., compatibility)
- 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 sets 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.[39] This information can be useful to aid FDA in determining the appropriate classification of your device. You may present suggested approaches to mitigate the underlying risks as part of the risk analysis.

- **Proposed Study Design(s)**

[39] For IVDs used in blood collection facilities, you may include an analysis of the impact of false negative and false positive results on donor deferral and management.

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;
- How you will utilize fresh, frozen, or otherwise preserved samples in the clinical studies; and/or
- A description of sample manipulation or processing steps and accessories required for these purposes.

- **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 and processing,
  - 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 equivocal results will be handled in the analysis).

  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 specimens (i.e., 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 you will analyze data (e.g., identify independent and dependent variables, provide interpretation criteria and your definition of positive, negative, or equivocal results).

- Description of how you determine and validate the cut-off or reference range.
- 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.

Appendix 2
Q-Sub Acceptance Checklist

Reviewer:
Office/Division/Branch:
Q Number:
Device Name:
Sponsor Name:
RTA Recommendation and Date:

		Yes	No
1.	Has the type of Q-Sub been identified in the cover letter or has sufficient information been provided in the submission to identify the type of Q-Sub? Choices are: a. Pre-Submission (Pre-Sub) b. Informational Meeting Request c. Submission Issue Meeting request d. Early Collaboration Meeting request (includes both Agreement and Determination meetings) e. Study Risk determination request Note: this checklist is not needed for PMA Day 100 Meeting requests.	☐ Continue with question 2	☐ Recommend Refuse to Accept
2.	Did the sponsor correctly identify the type of Q-Submission based on the definitions below? If not, can you determine the correct type of Q-Submission based on the definitions in 2a below? *If the answer to either question is yes, check "yes."*	☐ Go to the checklist specific to that Q-Sub type (see question 3 below)	☐ Go back to question 1 and answer "no"

2a.	Definitions **Pre-Submission (Pre-Sub)** • requests FDA's feedback on items necessary to guide product development and/or a future IDE, IND, or marketing submission • includes specific questions regarding review issues relevant to a planned IDE, IND, or marketing application *If the Q-Sub meets the definition of a Pre-Submission, go to page 3 and complete the Pre-*

Submission Checklist.

Informational Meeting Request

- requests a meeting or teleconference to provide an overview of ongoing device development when there are one or more submissions planned within the next 6-12 months; to familiarize the review team about new device(s) with significant differences in technology from currently available devices; or to otherwise provide information to FDA that the Agency may find useful
- contains NO requests for FDA feedback

If the Q-Sub meets the definition of an Informational Meeting Request, go to page 5 and complete the Informational Meeting Request Checklist.

Submission Issue Meeting Request

- requests a meeting or teleconference to discuss an active (i.e., under review or on hold) IDE, IND, or marketing submission for which FDA requested additional information related to that submission

If the Q-Sub meets the definition of a Submission Issue Meeting Request, go to page 6 and complete the Submission Issue Meeting Checklist.

Early Collaboration Meeting – Agreement Meeting

- requests a meeting with FDA to get the Agency's agreement on specified elements of a proposed study design (as outlined in the FD&C Act 520(g)(7))

If the Q-Sub meets the definition of Study Determination – Agreement Meeting, follow existing practices as described in Early Collaboration Meetings Under the FDA Modernization Act (FDAMA); Final Guidance for Industry and for CDRH Staff.

Early Collaboration Meeting – Determination Meeting

- requests a meeting with FDA to get the Agency's determination of the type of clinical trial needed to provide evidence of effectiveness (as outlined in the FD&C Act 513(a)(3)(D))

If the Q-Sub meets the definition of Study Determination – Determination Meeting, follow existing practices as described in Early Collaboration Meetings Under the FDA Modernization Act (FDAMA); Final Guidance for Industry and for CDRH Staff.

Study Risk Determination

- requests FDA's feedback on whether a planned study is a significant risk (SR) study, a non-significant risk (NSR) study, or exempt from IDE, or generally whether a planned study requires an IDE

If the Q-Sub meets the definition of Study Determination – Risk Determination, follow existing practices as described in Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors - Significant Risk and Nonsignificant Risk Medical Device Studies.

3.	Q-Sub type determined to be: ☐ Pre-Submission (*go to Pre-Sub checklist)* ☐ Informational Meeting Request (*go to Informational Meeting checklist)* ☐ Submission Issue Meeting Request (*go to Submission Issue Meeting checklist)* ☐ Early Collaboration Meeting – Agreement Meeting Request (*follow existing practices)* ☐ Early Collaboration Meeting – Determination Meeting Request (*follow existing practices)* ☐ Study Risk Determination (*follow existing practices)*

Contains Nonbinding Recommendations

Pre-Submission Checklist

Pre-Submission includes:		Yes	N/A	No
1.	Cover letter with contact information for sponsor and name of subject device.	☐		☐
2.	Table of contents	☐	☐	☐
3.	Device description includes information sufficient to understand what the proposed device is and how it works, such as: • a description of the device in text and with pictures, diagrams, and/or engineering drawings, as applicable • an explanation of the mechanism of action (i.e., how the device achieves its intended output or effect) • characteristics of the device output (if applicable) • description of the materials used in the device; • for an IVD, detailed technical description of the device including instruments, reagents, components, software, principles of operation, and accessories • an explanation of the scientific basis for the device and/or the expected clinical utility • for a device to be submitted in a 510(k), any anticipated predicate and a comparison of the device to the predicate device or a specific reference to a prior submission (e.g., Pre-Sub, Pre-IDE) where this information was previously provided and a statement that the information has not changed. *See the guidance for additional items that may be appropriate in the device description. (Note that inclusion of every item in the guidance is not required to accept the submission, only sufficient information to have a basic understanding of the device in question such that FDA's review can begin. More detailed information can be requested interactively.)*	☐		☐
4.	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 • statement of whether the device is intended for prescription and/or over-the-counter use • If an IVD device, includes a detailed draft of the intended use of the device including the intended use population, the analyte/condition to detect, and the assay methodology. or a specific reference to a prior submission (e.g., Pre-Sub, Pre-IDE) where the indication for use was previously provided and a statement that it has not changed.			
5.	A summary of any previous discussions or submissions (with submission number(s)) regarding the same device, if applicable.	☐	☐	☐
6.	An overview of planned product development, including an outline of nonclinical and clinical testing either planned or already completed.	☐		☐
7.	Specific questions for FDA feedback regarding review issues relevant to a planned IDE, IND, or marketing application	☐		☐
8.	Desired method for feedback	☐		☐

Did you check "yes" or "N/A" for all of the items in a white box (i.e., <u>not</u> shaded)?

☐ Yes. Recommend Acceptance (RTAA). If one or more of the shaded items are missing, contact the sponsor by phone or email to request this additional information (which can be added to the review record electronically).

☐ No. Recommend Refuse to Accept (RTA1).

Informational Meeting Request Checklist

Informational Meeting Request includes:		Yes	N/A	No
1.	Cover letter with contact information for sponsor and name of subject device.	☐		☐
2.	An agenda that specifies the topics for the meeting/telecon such that the appropriate FDA attendees can be identified?	☐		☐

Is the submission missing either of these items?

☐ Yes. Recommend Refuse to Accept.

☐ No. Recommend Acceptance. Proceed with scheduling the meeting or teleconference. Note that any additional information needed prior to the meeting/teleconference can be requested interactively through phone or email and added to the review record electronically).

Submission Issue Meeting Request

Submission Issue Meeting Request includes:		Yes	N/A	No
1.	Cover letter with contact information for sponsor and name of subject device.	☐		☐
2.	Document number of the active submission that is the subject of the meeting request (e.g., IDE, PMA, 510(k), HDE, IND, BLA)	☐		☐
3.	An agenda that specifies which deficiencies or other FDA requests for information are to be discussed such that the appropriate FDA attendees can be identified	☐		☐

Is the submission missing any of these items?

☐ Yes. Recommend Refuse to Accept.

☐ No. Recommend Acceptance. Proceed with scheduling the meeting or teleconference. Note that any additional information needed prior to the meeting/teleconference can be requested interactively through phone or email and added to the review record electronically).

Concurrence & Template History Page

Digital Signature Concurrence Table	
Reviewer Sign-Off	
Branch Chief Sign-Off	
Division Sign-Off	