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Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program

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Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

This draft guidance document is being distributed for comment purposes only.

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You should submit comments and suggestions regarding this draft document within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions about this document regarding CDRH-regulated devices, contact the CDRH Program Operations Staff (POS) at 301-796-5640. For questions about this document regarding CBER-regulated devices, contact the Office of Communication, Outreach, and Development (OCOD) at 1-800-835-4709 or 240-402-8010.

When final, this guidance will supersede *Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff* dated September 29, 2017.

U.S. Department of Health and Human Services

Food and Drug Administration

Center for Devices and Radiological Health

Center for Biologics Evaluation and Research

Preface

Additional Copies

CDRH
Additional copies are available from the Internet. You may also send an e-mail request to CDRH-Guidance@fda.hhs.gov to receive a copy of the guidance. Please use the document number 1677 to identify the guidance you are requesting.

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Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program

Draft Guidance for Industry and Food and Drug Administration Staff

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff or Office responsible for this guidance as listed on the title page.

I. Introduction[1]

The purpose of this guidance is to provide an overview of the mechanisms available to submitters through which they can request feedback from or a meeting with the Food and Drug Administration (FDA) regarding potential or planned medical device Investigational Device Exemption (IDE) applications, Premarket Approval (PMA) applications, Humanitarian Device Exemption (HDE) applications, Evaluation of Automatic Class III Designations (De Novo requests), Premarket Notification (510(k)) Submissions, Clinical Laboratory Improvement Amendments (CLIA) Waiver by Applications (CW), Dual 510(k) and CLIA Waiver by Application Submissions (Duals), Accessory Classification Requests, and certain Investigational New Drug Applications (INDs)[2] and Biologics License Applications (BLAs)[3] submitted to the Center for Biologics Evaluation and Research (CBER).

Throughout this guidance document, the terms "we," "us" and "our" refer to FDA staff from the Center for Devices and Radiological Health (CDRH) or CBER. "You" and

[1] The Office of Combination Products (OCP) was consulted in the preparation of this guidance.
[2] Applicable only to those devices that are regulated by CBER as biological products under Section 351 of the Public Health Service (PHS) Act and that also require submission of an IND prior to submission of a BLA. Such devices are generally those intended for use in screening donated blood for transfusion transmissible diseases.
[3] Applicable only to those devices that are regulated by CBER as biological products under Section 351 of the PHS Act, including those that do not require submission of an IND prior to the submission of the BLA. Such devices generally include those reagents used in determining donor/recipient compatibility in transfusion medicine.

"your" refers to the submitter. A "meeting" may be conducted in-person (face-to-face) or by teleconference. When there is a distinction between those two types of meetings, it will be noted in this guidance.

FDA's guidance documents, including this draft guidance, do not establish legally enforceable responsibilities. Instead, guidances 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 means that something is suggested or recommended, but not required.

II. Background

The pre-IDE program was established in 1995, to provide sponsors 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 PMAs, HDEs, De Novo requests, and 510(k) submissions, as well as to address whether a clinical study requires submission of an IDE.

To capture this evolution, the Secretary of Health and Human Services' (HHS) 2012 Commitment Letter to Congress regarding the Medical Device User Fee Amendments of 2012 (MDUFA III) included FDA's commitment to institute a structured process for managing these interactions, referring to them as "Pre-Submissions."[4] The Pre-Submission Guidance, published in February 18, 2014, implemented the broader Q-Submission (Q-Sub) Program, which includes Pre-Submissions (Pre-Subs), as well as additional opportunities to engage with FDA.

As part of the Medical Device User Fee Amendments of 2017 (MDUFA IV), industry and the Agency agreed to refine the Q-Sub Program with changes related to the scheduling of Pre-Sub meetings and a new performance goal on the timing of FDA feedback for Pre-Subs.[5] This guidance reflects those changes and clarifies other elements of the Q-Sub program.

III. Scope

The types of Q-Subs covered by this guidance in detail are listed in Sections III.A-D of this guidance. Some other submission types are noted solely to indicate that they are tracked with a "Q" number, and should be submitted following the basics for Q-Subs, while their details and processes are covered in separate guidance (see Sections III.E and F of this guidance). Finally, there are other interactions with FDA that are outside the scope of this guidance (Section III.G of this guidance):

[4] See 158 CONG. REC. S8277-S8281 (daily ed. Corrected December 20, 2012) (Letters from the Secretary of Health and Human Services Re: Medical Device User Fee Program), also available at http://www.fda.gov/downloads/MedicalDevices/NewsEvents/WorkshopsConferences/UCM295454.pdf.

[5] See 163 CONG. REC. S4729-S4736 (daily ed. August 2, 2017) (Food and Drug Administration User Fee Reauthorization), also available at https://www.fda.gov/downloads/ForIndustry/UserFees/MedicalDeviceUserFee/UCM535548.pdf.

A. Pre-Submissions (Pre-Subs)

A Pre-Sub includes a formal written request from an submitter for feedback from FDA that is provided in the form of a formal written response or, if the submitter[6] chooses, formal written feedback followed by a meeting in which any additional feedback or clarifications are documented in meeting minutes. Such a Pre-Sub meeting can be in-person or by teleconference as the submitter prefers.

A Pre-Sub provides the opportunity for a submitter to obtain FDA feedback prior to intended submission of a premarket submission (i.e., IDE, PMA, HDE, De Novo request, 510(k), Dual, BLA, IND), Accessory Classification Request or, CW. The request should include specific questions regarding review issues relevant to a planned IDE, CW or marketing submission (e.g., questions regarding nonclinical testing protocols; design and performance of clinical studies and acceptance criteria). A Pre-Sub is appropriate when FDA's feedback on specific questions is necessary to guide product development and/or submission preparation.

The program is entirely voluntary on the part of the submitter. 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, shorten total review times, and facilitate the development process for new devices. FDA believes that interactions provided within Pre-Subs are likely to contribute to a more transparent review process for FDA and the submitter. Our staff develops feedback for Pre-Subs by considering multiple scientific and regulatory approaches consistent with least burdensome requirements and principles, to streamline regulatory processes. FDA has found that feedback is most effective when requested prior to execution of planned testing. Issues raised by FDA in a Pre-Sub do not obligate submitters to addressing or resolving those in a subsequent submission, though any future submission related to that topic should discuss why a different approach was chosen or an issue left unresolved. Further, review of information in a Pre-Sub 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 considered as a whole, or if new information has become available since the Pre-Sub.

Note that for an Accessory Classification Request for an existing accessory type, FDA must provide an opportunity for the submitter to meet with FDA to discuss the appropriate classification of the accessory prior to submission as described in Section III.A of this guidance.[7] FDA is also willing to meet with manufacturers who intend to submit an Accessory Classification Request for a new accessory type. We recommend that requests for feedback regarding a planned Accessory Classification Request be submitted as a Pre-Sub. Submission procedures for the Accessory Classification Request itself are further described in Section III.E.

[6] For the purposes of this guidance document, manufacturers or other parties who submit an IDE, IND, CW, Dual, or marketing submission to the Agency are referred to as submitters.

[7] See section 513(f)(6)(D)(ii) of the FD&C Act.

B. Submission Issue Requests (SIRs)

A SIR is a request for FDA feedback on a proposed approach to address issues conveyed in a marketing submission (i.e., PMA, HDE, De Novo request, 510(k), Dual, or BLA) hold letter, CW hold letter, an IDE Letter, or an IND Clinical Hold letter. To further clarify the scope of SIRs, the following are considered appropriate marketing submission hold letters for the purposes of this guidance:

- Additional Information Needed for 510(k)s, De Novo requests, CWs, and Duals;
- Major Deficiencies, Not Approvable, Approvable with Deficiencies, Approvable Pending GMP, and Approval with PAS conditions for PMAs and HDEs;
- Complete Response Letter for Biologics License Applications (BLAs);

The SIR is intended to facilitate interaction between FDA and the submitter to quickly resolve or clarify issues identified in these letters so that projects can move forward. Submitters are expected to provide a formal response to any of these letters within the requested timeline regardless of whether a SIR is submitted.

Please note a SIR is not appropriate for discussing letters conveying final decisions, such as Not Substantially Equivalent, Withdrawals, and Deletions.

A SIR is not necessary for simple requests for clarification of issues in a letter that do not require the involvement of management. A SIR is also not necessary to discuss issues while a file is under active review.

C. Study Risk Determinations

A Study Risk Determination is a request for FDA determination for whether a planned medical device clinical study is significant risk (SR), non-significant risk (NSR), or exempt from IDE regulations as defined by the IDE regulations (21 CFR part 812). 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 FDA's guidance entitled "Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors Significant Risk and Nonsignificant Risk Medical Device Studies."[8] FDA is available to help the sponsor, clinical investigator, and IRB in making the risk determination. 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).

D. Informational Meetings

An Informational Meeting is a request to share information with FDA without the expectation of feedback. This information sharing can be helpful in providing an overview of ongoing device development (particularly when there are multiple submissions planned

[8] http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126418.pdf

within the next 6-12 months) and familiarizing the FDA review team about new device(s) with significant differences in technology from currently available devices. While FDA staff may ask clarifying questions during an informational meeting, they will generally be listening during the meeting and not prepared to provide any feedback.

E. Other Q-Submission Types Outside the Scope of this Guidance:

In addition to the Q-Sub types listed above, the Q-Sub program provides a mechanism to track interactions described in other FDA program guidances. Currently, in addition to the Q-Sub types above, the interactions that are tracked in the Q-Submission program include the following:

- PMA Day 100 Meetings as described in FDA's guidance entitled "Guidance on PMA Interactive Procedures for Day-100 Meetings and Subsequent Deficiencies."[9]
- Agreement and Determination Meetings as described in FDA's guidance entitled "Early Collaboration Meetings Under the FDA Modernization Act (FDAMA)."[10]
- Designation Request for a Breakthrough Device.[11]
- Accessory Classification Request:
    - For an Existing Accessory Type: to request appropriate classification of an accessory that has been granted marketing authorization as part of a premarket submission for another device with which the accessory is intended to be used. See the guidance entitled "Medical Device Accessories –Describing Accessories and Classification Pathway for New Accessory Types."[12]
    - For a New Accessory Type: to request appropriate classification of an accessory that has not been previously classified under the Federal Food, Drug, and Cosmetic Act (FD&C Act), cleared for marketing under a 510(k) submission, or approved in a PMA. Note that an accessory classification request for a new accessory type should be submitted together with the premarket submission for the parent device. However, the Accessory Classification Request will be tracked as a Q-Sub.

Policies and procedures for these other Q-Sub types can be found in their respective guidance documents. Further, as FDA works to create additional mechanisms to streamline the device development and review process, FDA may create additional Q-Sub types that follow the same principles and processes outlined in this guidance document.

F. Other Uses of the Q-Submission Program:

Please note that there are interactions that do not meet the definitions of the Q-Sub types described above and for which a new formal Q-Sub type has not been created. When a new Q-

[9] https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080191.pdf.

[10] https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073611.pdf.

[11] See section 515B(c) of the FD&C Act.

[12] https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm429672.pdf.

Sub type does not exist to track a particular type of interaction, FDA may use the Informational Meeting Q-Sub type as a vehicle to track those interactions. Examples of the types of interactions for which the Informational Meeting Q-Sub vehicle is currently used for tracking include:

- Request for feedback from CDRH on specific questions or cross-cutting policy matters from other government agencies, non-profits, trade organizations and professional societies. Note that FDA does not require a submission to meet with these groups, but is open to accepting them, should organizations voluntarily submit information in advance of the meeting for FDA's substantive review. [13]

- Request for feedback regarding development of a Medical Device Development Tool (refer to FDA's guidance entitled "Qualification of Medical Device Development Tools"). [14]

- Request for recognition of publicly accessible genetic variant databases (refer to FDA's guidance entitled "Use of Public Human Genetic Variant Databases to Support Clinical Validity for Genetic and Genomic-Based *In Vitro* Diagnostics. [15]

- Request for feedback regarding study design for a NSR or IDE exempt study for which the results are not intended to support a future IDE or marketing submission. A sponsor may wish to obtain FDA feedback on design elements of a clinical study that would not be eligible for discussion under a Pre-Sub according to the definition of a Pre-Sub.

- Combination product agreement meetings (CPAM) as defined under section 503(g)(2)(A) of the FD&C Act.

- Request for a waiver of an applicable requirement under 21 CFR part 812.28.

Although Informational Meetings as described in Section III.D of this guidance are generally intended for a submitter to provide information to FDA without the expectation of feedback from FDA, when Informational Meeting Q-Subs are used for tracking purposes when a formal Q-Sub type for that interaction has not been created, feedback may be provided as prescribed by the program for which the Informational Meeting Q-Sub type is being used.

[13] For these types of meetings with CBER staff, please see https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm106001.htm#indcont.

[14] https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm374432.pdf.

[15] https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM509837.

G. Interactions Not Within the Q-Submission Program:

There are several other means by which industry may obtain feedback from FDA which are outside the scope of the Q-Sub Program, including, but not limited to, the following:

- General FDA policy, procedure, or simple review clarification questions that can be readily answered by FDA staff (e.g., by the lead reviewer or Regulatory Project Manager (RPM)[16]).

- Discussion of issues identified while an IDE, IND or marketing submission is under active FDA review; such issues are addressed via interactive review as described in FDA's guidance entitled "Types of Communication During the Review of Medical Device Submissions."[17]

- Appeal meetings, which are described in FDA's guidance entitled "Center for Devices and Radiological Health Appeals Processes"[18] or for submissions made to CBER, "Guidance for Industry: Formal Dispute Resolution: Appeals Above the Division Level"[19] and CBER SOPP 8005: Major Dispute Resolution Process.[20]

- Procedures for obtaining a determination respecting the classification of a medical product as a drug, device, biological product, or combination product and Center assignment for medical products, i.e., a Request for Designation (RFD) or Pre-RFD. See FDA's guidances entitled "How to Write a Request for Designation (RFD)"[21] and "How to Prepare a Pre-Request for Designation (Pre-RFD)."[22] Please see the Office of Combination Products (OCPs) web site[23] for additional information and 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. Pursuant to section 513(g) of the FD&C Act, submitters must submit a 513(g) Request for Information to obtain information regarding the class in which a

[16] CBER submissions: Whenever the term "lead reviewer" is used in this guidance, the CBER equivalent, with respect to interactions with the submitter, is usually the Regulatory Project Manager (RPM); with respect to internal activities, the lead reviewer is usually equivalent to the Chairperson or Scientific Lead.

[17] https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM341948.pdf.

[18] https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM284670.pdf.

[19] https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126015.pdf.

[20] https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/UCM586107.pdf.

[21] https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM251544.pdf.

[22] https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM534898.pdf.

[23] http://www.fda.gov/CombinationProducts/default.htm.

device has been classified or the requirements applicable to a device under the FD&C Act. To provide additional information regarding 513(g) Requests for Information, FDA has issued a guidance entitled, "FDA and Industry Procedures for Section 513(g) Requests for Information under the Federal Food, Drug, and Cosmetic Act."[24]

IV. Q-Submission Program

The term "Q-Submission" or "Q-Sub" refers to the system used to track the collection of interactions described above. These are important opportunities for submitters to share information with FDA and receive input outside of the submission of an IDE, IND, marketing submission, or CW. The interactions tracked in the Q-Sub program may be used at different points along the total product life cycle for a device and are voluntary. For example, in a given product's development cycle, a submitter may wish to conduct an Informational Meeting, followed by a request for Breakthrough Device Designation, with later discussions to refine specific aspects of non-clinical and clinical testing through Pre-subs. Tracking these interactions as Q-Subs facilitates review and serves to document interactions for the record.

However, the number of Q-Subs and Q-Sub supplements submitted should be carefully considered to avoid confusion and unnecessary expenditure of both FDA and industry time and resources. The Q-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. If you intend to submit more than one Q-Sub to request discussion and/or feedback on additional topics for the same device, we suggest that your initial Q-Sub contain an overview of your expected submissions, including general time frames, if known. The intent is for FDA and the submitter to focus on the submitter's current priority. As such, for any given device, only one Q-Sub should be submitted at a time.

A Q-Sub cannot be withdrawn after feedback is provided and the file is closed; however there is no requirement for a follow-on premarket submission (i.e., IDE, PMA, HDE, De Novo request, 510(k), CW, Dual, Request for Accessory Classification, IND, or BLA).

FDA will keep the existence of Q-Subs confidential, 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).

A. General Q-Submission Considerations

1. Relating Q-Submissions to Future IDE, IND, CWs, and Marketing Submission(s) ("Related Submission(s)")

Many Q-Subs are followed by marketing submissions, IDEs, INDs, CWs, and/or supplementary Q-Sub interactions. These follow-on submissions are considered "related submissions" if they are for the same device and indications for use as the original Q-Sub. To

[24] https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM209851.pdf.

help link Q-Subs to their subsequent related submissions, the submitter should identify the relevant Q-Subs in the cover letter of the subsequent related submission. If the relevant Q-Subs are not identified in the cover letter of the subsequent related submission, they will not be linked in FDA's records. Therefore, there may be a delay in determining FDA's previous feedback, and the subject device may not be incorporated in any future analyses of Q-Sub program effectiveness.

In addition, the related submission should include a section that clearly references the previous communication(s) with FDA about the subject device (or similar device) and explains how any previous feedback has been addressed within the current submission. This discussion of previous feedback will streamline FDA review even if the submitter elects to address FDA feedback with alternative methods to those discussed during the previous interactions.

2. Combination Product Considerations

Requests for meetings regarding a combination product should be submitted to the lead center for the product,[25] in accordance with that center's corresponding processes. If CDRH or CBER receives a Q-Sub for a combination product, the lead center staff intends to notify the other center(s) involved in review of the combination product of its receipt and include the appropriate review staff from these other center(s) to ensure that the entire combination product review team is aware of the questions from the submitter and engaged, as needed, in providing comprehensive and aligned feedback. Please note that meetings and/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. However, FDA intends to meet with the submitter of a combination product within 75 calendar days after receiving such request. Please note that for products that are combination products, the submitter is responsible for identifying it as such in the submission.[26] FDA recommends this information be provided in the cover letter. Where submitters have determined they would like input from the Office of Combination Products (OCP), they may also submit a copy of the cover letter to OCP.[27]

B. Q-Submission Processes

The general processes for the Q-Sub program are outlined below, including submission tracking and meeting logistics as well as recommended content and timelines for each Q-Sub type.

1. Submission Content

[25] For more information on how combination products are assigned a lead Center for their premarket review and regulation, please see the following website on the RFD process https://www.fda.gov/CombinationProducts/RFDProcess/default.htm.

[26] See section 503(g)(8)(c)(v)(I) of the FD&C Act.

[27] The following website contains contact information for OCP https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OfficeofScienceandHealthCoordination/ucm2018184.htm.

To ensure appropriate log in and to facilitate review of a Q-Sub, the following should be included in a Q-Sub Cover Letter. Please be advised that your Q-Sub should be written in the English language.

- *Contact Information.* Company name, address, and contact person(s) including title(s), phone number(s), and email address(es). Note that contact information should be provided for the submitter as well as the correspondent (e.g., consultant), if different from the submitter.

- *Q-Sub Type.* Indication of which Q-Sub type is being requested. Note that only one Q-Sub type should be included in a particular submission.

- If a Q-Sub type includes the option for a meeting (e.g., a Pre-Sub, SIR, and Informational Meeting requests), please indicate the following to facilitate scheduling:
    i. A proposed agenda describing the topics to be presented and the estimated time for each agenda item;
    ii. The meeting format you are requesting (i.e., in-person or by teleconference; see Section 3.a. below);
    iii. Three (3) or more preferred dates and times when you are available to meet.
        a) While you should propose dates that suit your schedule, please keep in mind that FDA needs sufficient time to review the material submitted, hold internal discussions if needed, and identify a meeting time when the necessary team members are available.
        b) If your proposed dates do not allow for adequate preparation, FDA may not be able to accommodate your requested dates and will offer you alternative dates within an appropriate timeframe. Please refer to the timelines for Pre-Subs (see Section 4.a.2 below), SIRs (see Section 4.b.2 below), and Informational Meetings (see Section 4.d.2 below) in considering proposed dates that are likely to be accepted by FDA.
    iv. The planned attendees, including each attendee's position, or title, and affiliation.
        a) If you have not yet identified all of your attendees, you should indicate the type of subject matter experts you plan to invite. (See Section 3.b. below).
        b) FDA recommends that sponsors identify in their cover letter any appropriate FDA staff that are requested to attend the meeting if specific expertise may be needed (e.g., staff from other Centers).

The following should be easily identified within the Q-Sub:

- *Purpose.* The overall purpose of the Q-Sub including goals for the outcome of the interaction with FDA.

- *Device or Product Description.* An explanation of how the device functions, the basic scientific concepts that form the basis for the device, and the significant physical and

performance characteristics of the device. A brief description of the manufacturing process should be included if the manufacturing process may affect safety and/or effectiveness, and may therefore impact FDA's recommendations regarding device testing. The generic name of the device as well as any proprietary name or trade name should be included. Images, videos, and more detailed information may be included as appropriate in the submission itself.

- *Proposed Indications for Use or Intended Use*. including description of the disease(s) or condition(s) the device will diagnose, treat, prevent, cure or mitigate, including a description of the patient population for which the device is intended.

- *Regulatory History*. Listing of any relevant previous communications with FDA about the subject device including but not limited to any marketing submission, IDE, 513(g), and/or Q-Sub application numbers relevant to the subject Q-Sub. The submission itself should also include a brief summary of these previous FDA interactions and submissions, including feedback received and resolution of that feedback (or justification of alternative paths) as applicable.

Use of the CDRH Premarket Review Submission Cover Sheet[28] for submissions made to CDRH or CBER is highly recommended to facilitate correct login and prompt routing to the appropriate review group.

You must submit an eCopy of your Q-sub under section 745(A)(b) of the FD&C Act. For more information on eCopy and the submission process, please refer to https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/ucm370879.htm, including the guidance entitled "eCopy Program for Medical Device Submissions."[29] In addition to the eCopy guidance, for Q-Subs for products regulated in the Center for Biologics Evaluation and Research (CBER), additional information regarding electronic submission can be located at the following website https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm385240.htm.

2. FDA Submission Tracking

FDA assigns a unique identification number to all Q-Subs as described below.

- *Original*. An original Q-Sub is the first Q-Sub submitted to FDA to discuss a given device and its indications for use, 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.

  Original Q-subs submitted to CDRH will be assigned a number starting with "Q" followed by two digits representing the year, and four digits representing the order in

[28] See Form 3514, https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM080872.pdf.
[29] https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM313794.pdf.

which the request was received during that calendar year. For example, the first original Q-Sub received by CDRH in January of 2018 will be identified as "Q180001." FDA will send an acknowledgement letter via e-mail to the contact identified in the Q-Sub cover letter that contains the unique tracking number and date received by the Document Control Center (DCC). Any future communications regarding your Q-Sub should include this unique Q-Sub identifier.

Because of organizational differences between CBER and CDRH, the process described in the preceding paragraph is not applicable to submissions sent to CBER. 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 RPM who will provide you with a BQ number and who will be your contact for all additional communications.

- *Supplement*. A Q-Sub supplement is any new request for feedback and/or a meeting about the same or similar device and indications for use as an original Q-Sub that already exists. For example, it may be appropriate to request an Informational Meeting to familiarize the review team with the new device design, then submit a Pre-Sub to request feedback on nonclinical testing, then a Study Risk Determination Q-Sub for the pivotal clinical study, all for the same combination of device and indications for use. The first Informational Meeting in this example would be the original Q-Sub, while the Pre-Sub and Study Risk Determination Q-Sub would be tracked as supplements to that original Q-Sub.

  At CDRH, each supplement is tracked by appending "/S" after the original followed by a three-digit sequential number, e.g., the first supplement to Q180001 will be identified as "Q180001/S001." At CBER, "S" is not used, only the slash (/) is added.

- *Amendment. A Q-Sub amendment is any additional information relevant to the original Q-Sub or Q-Sub supplement that does not represent a new request for feedback and/or meeting. This additional information could include presentation slides, meeting minutes, minor clarifications, or requests to change contact information.*

- If you need to change contact information, such as submitter organization or correspondent (e.g., consultant) organization, you should submit a Q-Sub amendment to your original clearly stating the change. Note that if you need to change the submitter, the Q-sub submitter of record (the submitter recorded in our system) should provide a letter authorizing the change in submitter. If you do not need to change the submitter, but want to change the correspondent, there are two possible scenarios: 1) changing the correspondent organization and 2) changing just the correspondent contact person. If the submitter wants to change the correspondent organization, such as adding or removing the use of a consultant, then the submitter should submit the change stating the new correspondent organization and providing the name, email address, and phone number of the new primary contact in that organization. If you would like to use a different correspondent contact person for a given supplement, you do not have to

submit an amendment; you can indicate the appropriate correspondent contact person when yo submit that supplement.

- At CDRH, each amendment is tracked by appending "/A" after the original or supplement to which it applies. For example, the first amendment to Q180001 will be identified as "Q180001/A001," while the first amendment to Q180001/S001 will be identified as "Q180001/S001/A001." At CBER, "A" is not used, only the slash (/) is added.

3. Meeting Information

Meetings allow for an open discussion and exchange of technical, scientific, and regulatory information that can help build a common understanding of FDA's views on clinical, nonclinical, or analytical studies related to an IDE, or marketing submission. During a Q-Sub meeting, FDA will be prepared to discuss the contents of the Q-Sub as well as any written feedback the Agency has already provided. Please note that we are generally unable to comment on new information provided immediately prior to or during a meeting. If a submitter would like feedback on new information, such a request should be submitted as a supplement to the Q-Sub to allow adequate time for review, written feedback, and discussion of the new material, as appropriate.

Submitters that request a meeting 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) Meeting Format

If desired, FDA is available to meet in-person or via teleconference. In-person meetings can be helpful in providing live demonstrations, but may take longer to schedule due to conference room availability. Generally, teleconferences may be more easily scheduled. For an in-person meeting, you should inform the lead reviewer or meeting coordinator of any audiovisual equipment you will need, such as conference phone or LCD projector or similar. The meeting coordinator or lead reviewer will reserve the room and arrange for any audiovisual equipment you may have requested. Please note visitors are not allowed access to any FDA/HHS information technology systems. This includes attaching USB cables, thumb drives, and any network-connected FDA/HHS equipment.

Please note that, in our experience, one (1) hour is adequate for most meetings. If you believe that more than one hour is needed, please provide a rationale for the duration you propose. You should also refer to that rationale and confirm the duration requested when the meeting coordinator or lead reviewer schedules your meeting.

b) Meeting Attendees

FDA will always attempt to ensure the appropriate FDA staff is 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, other members of management and program staff may also attend. You can help to ensure that appropriate FDA staff is 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.

All non-U.S. citizens attending a meeting in an FDA facility are subject to additional security screening. You should inform the meeting coordinator or lead reviewer prior to the meeting date and work with them to ensure the appropriate information is available and provided. It generally takes about two weeks to process requests for foreign visitors.

You are invited and encouraged to include any additional outside individuals (e.g., Centers for Medicare & Medicaid Services (CMS), private payers, NIH grant reviewers) in your Q-Sub meetings, as appropriate. Including additional representatives may be helpful in maintaining transparency, efficiencies, and consistency among the various stakeholders for your device. For submissions to CDRH, the Payer Communications Task Force may be able to assist with engaging payers. Additional information is on the Task Force's website.[30] However, you are responsible for coordinating the appropriate invitations and scheduling for other external stakeholders or for interactions with payers on Q-Subs reviewed in CBER.

c) Meeting Minutes

The submitter is responsible for drafting meeting minutes for all Q-Sub meetings. You should have a member of your team assigned to take meeting minutes, to be provided for FDA review following the meeting. At the beginning and end of the meeting, the submitter will affirmatively state that they will draft minutes and provide them to FDA within 15 calendar days. Industry attendees are not permitted to record the meeting by audio or video means. 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.

The draft meeting minutes should be submitted to FDA 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 appropriate tracking of the meeting minutes and documentation in the official record.

The meeting minutes should be an accurate reflection of the meeting discussion. Rather than being a transcript of the meeting, the minutes should summarize the meeting discussion, document how substantial or complex issues were resolved, and include agreements and any

[30] https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHInnovation/ucm456149.htm.

action items. Additional information or follow-up items that were not part of the meeting discussion should not be included in the meeting minutes.

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. If FDA does edit your draft minutes, FDA will email those to you in a timely manner (generally within 30 days). These edits may include post meeting notes to follow up on action items identified and agreed upon during the meeting. Minutes edited by FDA 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, within 15 calendar days, 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 submitter. Such differences of opinion should be addressed in additional Q-Sub meetings if both the submitter and FDA believe that further discourse on such an issue would be productive.

4. Processes by Q-Submission Types

Each Q-Sub type has a different review process including timeline and recommended content, which are detailed below.

a Pre-Submission

1) Additional Recommended Submission Contents

In addition to the general information that should be included in a cover letter for any Q-Sub type to ensure appropriate login and submission tracking (see Section IV.B.1), the following information should be included in a Pre-Sub:

- *Planned Follow-On Submission.* Please clearly indicate what type of future submission (IDE, IND, CW, Accessory Classification Request, or marketing submission) is the focus of your Pre-Sub questions to help direct FDA's feedback.

- *Background Information:* Please include sufficient background information and supporting documents to allow FDA to develop feedback for the Pre-Sub questions you pose. This information might include literature articles, full device description with engineering drawings, proposed labeling, videos, and/or red-lined protocol revisions depending on the specific questions for which you are requesting feedback.

While the importance of a complete background package cannot be overstated, it should also be noted that submission of extraneous information can be counterproductive. We recommend that you keep your submission targeted and focused.

- *Specific Questions.* A Pre-Sub should include clear, specific questions regarding review issues relevant to a planned IDE, IND, CW, Accessory Classification Request, or marketing submission (e.g., questions regarding nonclinical and clinical testing protocols or data requirements) to allow FDA and the submitter to focus their efforts on issues most relevant to moving a project forward. You may wish to describe your perspective on the questions you provide FDA to inform FDA's review.

  We recommend carefully considering the number of questions and extent of feedback requested in a single Pre-Sub to ensure that FDA has sufficient time to provide an in-depth response to each question. In general, FDA has found it difficult to address more than 3-4 substantial questions in a single Pre-Sub.

  Additional guidance regarding common types of questions submitted in Pre-Subs is provided below:

  - *Study Protocols*
    Please note that resource constraints do not permit FDA to prepare or design particular study plans. If a submitter would like FDA's feedback on a protocol, they should submit a proposed outline, with a rationale for the chosen approach.

    If the Pre-Sub is for a nonsignificant risk device study, IDE exempt device, CW, Dual, or a study you plan to conduct outside the US (OUS) to support a marketing submission, the submitter should consider submitting the entire protocol through the Pre-Sub process prior to initiating the study, particularly if it raises unique scientific or regulatory considerations.

  - *Review of Data*
    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.

  - *Regulatory Approach*
    Please note that under the Pre-Sub program, FDA is able to provide *general* feedback regarding regulatory strategy and approach. For example, whether a cleared 510(k) device or granted De Novo has the potential to serve as a predicate for a proposed device and indications for use. A formal written request for classification of a device and indications for use requires a 513(g)

Request for Information.[31] See Section III.G of this guidance for information on how to clarify whether a medical product is considered a device, drug, biologic, or combination product and/or Center assignment for medical products.

Examples of questions that lead to productive Pre-Sub interactions are provided in Appendix 2 of this guidance.

2) Review Process

The review process for a Pre-Sub, including timelines outlined in the MDUFA IV Commitment Letter, is described below.

- *Acceptance Review.* Within 15 calendar days of receipt of a Pre-Sub that includes a valid eCopy, FDA staff will conduct an acceptance review using the Acceptance Checklist (see Appendix 1 – Pre-Submission (Pre-Sub) Acceptance Checklist). The submitter will receive notification regarding whether or not the submission has been accepted for review as well as the contact information for the lead reviewer. If a Pre-Sub requesting a meeting is accepted, this notification will also either confirm one of the submitter's requested meeting dates or provide two alternative dates that are prior to day 75 from receipt of the submission. For a determination that the request does not qualify as a Pre-Submission, FDA staff will obtain concurrence from management of the decision to Refuse to Accept (RTA). The notification to the submitter will include the reasons for refusal.

  The submitter may respond to an 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 will conduct the acceptance review again following the same procedure within 15 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 Acceptance Checklist.

- *Scheduling of Meeting.* FDA will attempt to schedule a meeting on one of the submitter's requested meeting dates, if feasible. Meeting dates between 60-75 days following FDA receipt of your submission are most likely to be feasible. If FDA cannot accommodate one of the submitter's requested dates, FDA will offer at least two alternative dates that are prior to 75 days from the receipt date of an accepted submission. FDA intends to reach agreement with the submitter regarding a meeting date within 30 days from receipt of an accepted submission. For all requests for meetings that do not have an agreed upon meeting date scheduled by 30 days from receipt of an accepted submission, an FDA manager will contact the submitter to resolve scheduling issues by the 40th day.

- *Feedback.* Written feedback will be provided to the submitter by email or fax and will include: written responses to the submitter questions; FDA's suggestions for additional

[31] https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm209851.pdf.

topics for the meeting or teleconference, if applicable; or, a combination of both. FDA intends to follow the timeline below for providing feedback to a Pre-Sub.

- Pre-Sub Written Feedback: If no meeting is requested, written feedback will be provided within 70 days of receipt and will serve as the official record of the Agency's feedback.

- Pre-Sub Meeting: If a meeting is requested, written feedback will be provided at least 5 days prior to the scheduled meeting, and no later than 70 days from receipt of the accepted Pre-Sub. If all the submitter's questions are addressed to the submitter's satisfaction, the submitter may cancel the meeting and the written response will serve as the official record of the Agency's feedback. If a meeting is held, the meeting minutes will supplement the written feedback as part of the official record of the Agency's feedback.

FDA will generally be unable to review and respond to additional information prepared by the submitter and provided to FDA between receiving FDA written feedback and holding the meeting or during the meeting. Any information requiring additional internal FDA review should be submitted as a supplement to the Pre-Sub. It is, however, appropriate to narrow your agenda to focus on specific questions or topics in the feedback.

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, IND, or marketing submission is consistent with that provided in the Pre-Sub, and that the data in the future submission, changes in the science, or changes in the standards of care 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 a reasonable assurance of safety and/or effectiveness, substantial equivalence, or other relevant regulatory decision, 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.[32] Further, FDA intends to work with the submitter to address any new issues raised by the change, taking into consideration the stage of device development, where possible.

[32] The CDRH SOP: Decision Authority for Additional or Changed Data Needs for Premarket Submissions should be followed: https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHReports/ucm279288.htm.

Because clinical practice is constantly evolving, we recommend that if more than one (1) year has passed since our last feedback on key clinical trial design elements with no submission to the Agency, submitters should contact the review division to confirm that our previous advice is still valid. This can be accomplished through a phone call to the lead reviewer; a new Pre-Sub is not needed.

b. Submission Issue Request (SIR)

1) Additional Recommended Submission Contents

In addition to the general information that should be included in a cover letter for any Q-Sub type to ensure appropriate login and submission tracking (see Section IV.B.1), the following information should be included in a SIR:

- *Specific Questions.* A SIR should include clear, specific questions regarding review issues relevant to the planned response to the pending marketing submission hold letter (e.g., questions regarding non-clinical and clinical testing protocols or data requirements), IND Clinical Hold, or IDE letter, including identification of the deficiencies to be discussed, in order to focus FDA and submitter efforts on issues most relevant to moving a project forward.

  If a submitter would like feedback on plans for collection of new data to address a review issue, the submitter should propose a protocol with a rationale for the chosen approach. Please note that resource constraints do not permit FDA to prepare or design studies. In addition, requests for a pre-review of data are generally not appropriate for a SIR. However, if 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.

- *Preferred Feedback Format:* In the cover letter, the submitter should specify their preferred mechanism for obtaining FDA feedback (i.e., written feedback or a meeting) on their SIR.

2) Review Process

- *Acceptance Review.* There is no Acceptance review for a SIR.

- *Feedback.* In the spirit of the MDUFA Shared Outcome goals for Total Time to Decision on most marketing submissions, FDA is committed to resolving review issues promptly and will place added emphasis when Industry similarly works expeditiously to address such issues.[33] Accordingly, FDA intends to prioritize review of SIRs submitted within 30 days of the marketing submission hold, IND Clinical Hold, or IDE letter. This allows

[33] See 163 CONG. REC. S4729-S4736 (daily ed. August 2, 2017) (Food and Drug Administration User Fee Reauthorization), also available at https://www.fda.gov/downloads/ForIndustry/UserFees/MedicalDeviceUserFee/UCM535548.pdf.

FDA to leverage the familiarity with a recent review without the need to re-review the issues. This also incentivizes prompt resolution of issues by both FDA and Industry in order to achieve the MDUFA Shared Outcome goals for Total Time to Decision. FDA intends to provide feedback (either via written feedback or through a teleconference, or meeting, at the request of the submitter) according to the timelines below, to the extent resources permit.

- Submission Issue Request A: If a Submission Issue Request is received within 30 days of FDA's marketing submission hold, IND Clinical Hold letter, or IDE letter, the FDA team will aim to provide feedback within 21 days, as resources permit.

- Submission Issue Request B: If a Submission Issue Request is submitted more than 30 days after FDA's letter, FDA will aim to provide feedback within 70 days, as resources permit.

c. Study Risk Determination Requests

1) Additional Recommended Submission Contents

In addition to the general information that should be included in a cover letter for any Q-Sub type to ensure appropriate login and submission tracking (see Section IV.B.1), a Study Risk Determination Request should include the protocol for the proposed clinical study.

2) Review Process

- *Acceptance Review*. There is no Acceptance review for a Study Risk Determination request.

- *Determination.* Once a determination is made, FDA will issue a letter to the submitter indicating whether the study is exempt, or, if not exempt, is considered Significant Risk (SR) or Not Significant Risk (NSR). You may copy the letter to submit it 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. Informational Meeting

1) Additional Recommended Submission Contents

There is no specific additional information requested for Informational Meeting requests beyond the general information that should be included in a cover letter for any Q-Sub type to ensure appropriate login and submission tracking (see Section IV.B.1). As Informational Meeting requests may be used for multiple purposes (see Section III), submitters should consider any additional information relevant to the goals of their submission.

2) Review Process

- *Acceptance Review*. There is no Acceptance review for an Informational Meeting.

- *Meeting*. FDA aims to hold an Informational Meeting within 90 days of receiving the submission, as resources permit.

5. Other Q-Sub Types or Uses of the Q-Sub Program

Please refer to the respective program resources for any additional submission contents and timeline information relevant to PMA Day 100 Meetings,[34] Agreement and Determination Meetings,[35] Designation Requests for a Breakthrough Device,[36] Qualification of Medical Device Development Tools,[37] Accessory Classification Requests,[38] requests for recognition of publicly accessible genetic variant databases,[39] CPAMs,[40] and requests for waivers under 21 CFR 812.28.[41]

Policy and procedural information regarding any Q-Sub types that will be created in the future will be described through appropriate mechanisms so that timelines and submission expectations are known.

[34] https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080191.pdf.
[35] https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073611.pdf.
[36] See section 515B(c) of the FD&C Act.
[37] https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM374432.pdf.
[38] https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm429672.pdf.
[39] https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM509837.
[40] Defined under section 503(g)(2)(A) of the FD&C Act.
[41] https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM597273.

Appendix 1 – Pre-Submission (Pre-Sub) Acceptance Checklist

Reviewer:
Office/Division/Branch:
Q-Number:
Device Name:
Submitter Name:
RTA Recommendation:
Date of RTA Recommendation:

		Yes	No
1	Has the submitter provided a purpose or goal for their Pre-Sub?	☐	☐
2	Has the submitter identified device(s) or other product(s) to be discussed in their Pre-Sub?	☐	☐
3	Has the submitter provided questions that request FDA feedback?	☐	☐
4	Does the submission indicate that the submitter intends to submit a future IDE, CLIA Waiver by Application, IND, or marketing submission related to the feedback being requested?	☐	☐

☐ No for question 1, 2, 3, or 4 → Recommend Refuse to Accept Pre-Submission (RTA1) or consider conversion to appropriate Q-Sub type
☐ Yes for questions 1, 2, 3, and 4→ Continue to questions 5 and 6

		Yes	No
5	Do the provided questions pertain to a file under active review?	☐	☐
6	Do the provided questions relate to a marketing submission or CLIA hold letter, [42] an IND Clinical Hold letter, or an IDE letter?	☐	☐

☐ No for questions 5 and 6→ Recommend Accept (RTAA)
☐ Yes for question 5 → RTA1 and resolve during interactive review of the open file
☐ Yes for question 6 → Convert to Submission Issue Request (SIR)

[42] FDA considers the following to be marketing submission hold letters or CLIA hold letters:

- Additional Information Needed for 510(k)s, De Novos requests, CLIA Waivers by Application, and Dual 510(k) and CLIA Waiver by Application Submissions
- Major Deficiencies, Not Approvable, Approvable with Deficiencies, Approvable Pending GMP, and Approval with PAS conditions for PMAs and HDEs
- Complete Response Letter for BLAs

- Note that final decisions, such as Not Substantially Equivalent, Withdrawals, and Deletions are not considered marketing submission hold letters.

Appendix 2 – Example Pre-Sub Questions

A Pre-Sub should contain clear, specific questions regarding review issues relevant to a planned IDE, CW, IND, or marketing submission in order to focus FDA and submitter efforts on issues most relevant to moving a project forward. In FDA's experience, questions that lead to productive Pre-Sub interactions share the following characteristics:

- Questions request specific feedback on a provided proposal (e.g., an animal model is proposed, including rationale, and FDA feedback is requested on the acceptability of the animal model)
- Questions have considered and include reference to applicable guidance documents, standards and previous discussions with FDA (e.g., chemical characterization testing is proposed with citations to relevant biocompatibility guidance document and standards as well as feedback FDA provided in previous Pre-Sub interactions)
- Questions clearly articulate a desired outcome including indications for use or labeled uses (e.g., FDA feedback is requested on clinical study endpoints, inclusion criteria, and follow up duration given that the study is intended to expand the currently approved indications for use from prescription use only to over the counter use)
- Questions are timed to inform future device development and submission preparation (e.g., prior to conducting fatigue testing, a submitter requests feedback regarding proposed pre-conditioning procedures)
- Questions do not request decisions regarding approval or clearance of a future IDE, CW, IND, or marketing submission; that is, a question should not ask "Will an IDE that includes results from the proposed testing be approved?"
- Questions do not provide data unless necessary as supportive context for a specific proposal; that is, a question might provide limited bench, animal or clinical study data, but only to provide FDA with the needed background information to develop feedback in response to a specific proposal (e.g., one page of preliminary feasibility clinical study results are provided when FDA feedback is requested for proposed pivotal study endpoints)
- Questions do not ask FDA to design a study or indicate how a submitter should proceed; that is, a question should not ask "What should my clinical study design be?"
- Questions do not request formal regulatory determination; that is, a question should not ask "Is my device a Class II medical device to be regulated under CFR 892.2050?"

The following are examples of questions, provided by review topic category, expected to lead to productive Pre-Sub interactions.

<u>Regulatory Strategy Questions</u>

- Are there concerns with the predicate device proposed?
- Can we obtain FDA's feedback and guidance on pursuing a De Novo request for classification pathway given that there is not a currently marketed device that we believe could serve as predicate under the 510(k) pathway?
- Based on the regulatory strategy provided, does FDA agree, based on the discussion provided, that additional clinical data is not needed to support a future 510(k)?

<u>Indications for Use/Intended Use Questions</u>

- Does FDA have any concerns with our proposal to label the described device as over the counter?

- Does FDA agree with the proposed definition of drug-resistant hypertension provided in the draft indications for use statement?
- Does the Agency agree with the proposed size range offered for the new device, based on the intended use?

Clinical Study Questions

- Does FDA have any comments on the provided OUS study protocol regarding its ability to support a future HDE?
- Does FDA agree with the revised clinical study designs, statistical analysis and acceptance criteria included in this Pre-Sub supplement?
- Are the primary and secondary analyses appropriate for the Indications for Use for the monitoring indication proposed?

Labeling Questions

- Does FDA agree with the proposed test plan in support of MR Conditional labeling for 1.5T scanners with an exclusion zone between the neck and groin?
- We intend to label our device for re-use if the attached cleaning instructions are followed. The test plan to support this label is provided in Attachment B. Does FDA agree with this plan?

Reprocessing, Sterilization & Shelf Life Questions

- Does FDA have any comments about the methods described in the Microbiology protocol "Microbiology Study Protocol" included in Appendix 3?
- Does FDA concur that accelerated testing outlined in Appendix 2 conducted to represent 1 year shelf life is sufficient for an IDE with real time testing provided in the PMA?
- To address FDA's deficiency regarding our sterilization validation, we propose using Small Lot Release in accordance with Annex E of ISO 11135-2014. Does FDA have objections?
- Does FDA agree with our recommendation to low level disinfect the cannula device between uses?

Benchtop Performance Testing Questions

- Does FDA agree with the provided justification for the proposed worst case comparison testing?
- In the event that the prospective collection does not meet the protocol's intended number of specimens of a given type, we propose to use retrospective, characterized (banked) specimens to ensure these numbers are achieved. Is this approach acceptable to FDA?
- We have provided a justification of the worst-case testing volume that will be used, and provided an analysis of the sensitivity of the test, as requested. Does FDA find this justification and analysis adequate to support using the methodology described in our testing protocol? If not please provide further guidance.
- Does the Agency agree with our approach to use the average of valid measurements of the five replicate measurements?
- We have provided a response to FDA's question about sample sizes used in the in vitro test, along with a justification based on a power analysis. Is this plan acceptable? If not please provide further guidance.

Animal Study Questions

- Does FDA concur that the revised GLP Study design is sufficient to address potential device risks and support initiation of a pivotal clinical trial?
- Is our alternative approach to an animal study appropriate?
- Please advise if FDA believes that additional animal studies outside of those already conducted (and described in this submission) are recommended to support a future marketing application.
- Does the agency agree that the proposed animal study is designed to provide a sufficient assessment of the local tissue and systemic response?
- Is the animal model proposed appropriate based on the proposed intended use?
- Are the proposed animal study endpoints and follow up schedule appropriate?

Biocompatibility Questions

- We propose to conduct the biocompatibility testing identified in Tables 7-9 on only the largest model dialyzer. Does FDA concur with the testing protocol?
- We propose to conduct chemical characterization (described in Appendix 1) in lieu of chronic implantation testing. Please provide any comments on the acceptability of this approach.
- Is our justification for not conducting carcinogenicity studies adequate?
- Is our alternative test method to the material-mediated sensitization testing, which does not use a traditional rabbit model but an *in vitro* alternative, acceptable?

Software/Firmware Questions

- Does FDA agree that our software/instrument is a moderate level of concern and that the level of documentation that will be included in an upcoming marketing submission is consistent with FDA's recommendations provided in FDA's guidance entitled "Guidance for the Content of Premarket Submission for Software Contained in Medical Devices?"[43] as part of the upcoming device submission?
- Does FDA expect any further data validating functional operation of alerts and alarms in real or simulated circumstances beyond that recommended in FDA's guidance entitled "Guidance for the Content of Premarket Submission for Software Contained in Medical Devices?"[44] If so, can FDA give us additional guidance on what they might like to see?
- Does FDA agree that the software documentation defined in Section 4.2 of this Pre-Sub does not need to be included in the PMA supplement for the device as it was previously reviewed and approved in other PMA supplements (i.e., the PMA supplement will reference previously submitted information)?

Human Factors Questions

- Does the agency have comments on our proposed human factors engineering process?
- Is the attached use-related risk analysis plan adequate? Does the agency agree that we have identified all the critical tasks?
- Does the agency agree with our proposed test participant recruitment plan for the human factors validation testing?

[43] https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089593.pdf.
[44] https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089593.pdf.

Appendix 3 – Example of Meeting Minutes

To improve understanding of what FDA expects to see in meeting minutes for Q-Subs, the following example is provided. While submitters are committed to taking and submitting meeting minutes, use of this format is optional.

As noted above, when you submit your meeting minutes, you should also include a copy of the slides you presented at the meeting.

Meeting Minutes

Submission Number: e.g., QYYNNNN or QYYNNNN/SNNN
Submission Type: e.g., Pre-Sub Meeting, Submission Issue Request
Product Name: Test ABC Device/Dx
Sponsor/Submitter: Company name
Meeting Date/Time: e.g., January 1, 2014; 2:00 pm
Meeting Format: Face-to-Face or Teleconference
Date FDA Feedback was Sent: e.g., December 25, 2013

FDA Attendees:
(If you do not have this information, please contact your CDRH lead reviewer or CBER regulatory project manager via interactive review)
Full Name Title; Organization
Full Name Title; Organization
et cetera

Company Attendees:
(Please include titles and company affiliation if more than one)

Discussion:
(*Note: Please include a summary of key questions and decisions; this is not intended to be a transcript of the meeting, but should include any agreements reached and any items that require further consideration, as applicable. It is suitable to indicate, for example, "after some discussion, it was decided that the pre-clinical testing should address …")*

(Please refer to FDA or Company name, as appropriate, rather than specific individuals.)
(If your presentation included any demonstrations, samples, models, et cetera, please do include a note to that effect.)

Company X affirmed that it would be taking meeting minutes for this meeting.

Company X presented its agenda for the meeting, including anticipated time allotted for each item.

Company X briefly reviewed its purpose in submitting this Q-Sub and the current state of its device development.

Company X indicated that, of the 5 questions it had posed in submitting this Q-Sub, it wanted to focus the meeting on questions 1, 3, and 5, since FDA's responses to questions 2 and 4 appeared to be sufficient.

Company X also wanted to clarify some of the additional feedback FDA had provided.

Question 1: (Your original question as submitted to FDA)
FDA Response to Question 1: (Optional) (Include the written response FDA provided prior to the meeting) (Minutes should capture if the company provided clarification or justification to anything in the original submission, if there was any clarification or justification to FDA's written feedback, and if the company agreed or stated what its next steps would be. Do not capture the discussion verbatim. Clearly identify agreements and/or disagreements that were reached by FDA and the submitter during the discussion related to this specific question.)

Question 3:
…
Question 5:
…
Additional Feedback Item 1:
…

Decisions made and/or agreements reached:
KEY decisions or agreements should be listed succinctly here for easy reference later.

Reference the question # relevant to the decision or agreement that was reached during discussion of a specific question.

Action Items and Meeting Closure:
Company X indicated that it had taken meeting minutes and would provide those to FDA within 15 days as an amendment to this Q-Sub.

(If Company X indicated its next priority for a future FDA premarket submission, that would be useful to note)

(If either FDA or the company agreed to any action items post-meeting, beyond submitting the meeting minutes, those should be noted with a brief description, owner (FDA or company), and projected date for completion.)