Contains Nonbinding Recommendations

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

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Guidance for Industry and Food and Drug Administration Staff

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For questions about this document regarding CDRH-regulated devices, contact ORP: Office of Regulatory Programs/DRP1: Division of Submission Support 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, or by email at ocod@fda.hhs.gov.

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See additional PRA statement in Section IV of this guidance.

Preface

Public Comment

You may submit electronic comments and suggestions at any time for Agency consideration to https://www.regulations.gov. Submit written comments to the Dockets Management Staff, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD 20852-1740. Identify all comments with the docket number FDA-2018-D-1774. Comments may not be acted upon by the Agency until the document is next revised or updated.

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Contains Nonbinding Recommendations

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

Guidance for Industry and Food and Drug Administration Staff

This guidance represents 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 document is to provide an overview of the mechanisms available to submitters through which they can request interactions with the Food and Drug Administration (FDA) related to medical device submissions. These interactions can include written feedback and/or a meeting related to potential or submitted 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) and Biologics License Applications (BLAs) submitted to the Center for Biologics Evaluation and Research (CBER)) (specifically, INDs and BLAs for devices that are regulated as biological products under section 351 of the Public Health Service (PHS) Act).

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

As part of the Medical Device User Fee Amendments of 2017 (MDUFA IV), industry and the Agency agreed to refine the Q-Submission (Q-Sub) Program with changes related to the scheduling of Pre-Submission (Pre-Sub) meetings and a new performance goal on the timing of

[1] The Office of Combination Products (OCP) was consulted in the preparation of this guidance.

FDA feedback for Pre-Subs.[2] As part of the Medical Device User Fee Amendments of 2022 (MDUFA V), these goals were further refined.[3] The Agency also committed to issuing a draft guidance update to include additional information to assist submitters and review staff in identifying the circumstances in which a submitter's question is most appropriate for informal communication instead of a Pre-Sub.

In general, FDA's guidance documents 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 guidances means that something is suggested or recommended, but not required.

II. Scope

The types of Q-Subs covered by this guidance in detail are listed in Sections II.A-E 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 processes for Q-Subs, while their details and processes are covered in separate guidance documents (see Sections II.F and G of this guidance). Finally, there are other interactions with FDA that are outside the scope of the Q-Sub program (Section II.H of this guidance).

A. Pre-Submissions (Pre-Subs)

A Pre-Sub includes a formal written request from a submitter[4] for feedback from FDA that is provided in the form of a formal written response or, if the submitter chooses, formal written feedback followed by a meeting. As described in the MDUFA V commitment letter, discussion that occurs during the meeting is summarized in meeting minutes that are drafted by the submitter and submitted for FDA review.

A Pre-Sub provides the opportunity for a submitter to obtain FDA feedback prior to an intended premarket submission (which, for purposes of this guidance, refers to an IDE, PMA, HDE, De Novo request, 510(k), CW, Dual, Accessory Classification Request, BLA, or IND). The request should include specific questions regarding review topics relevant to a planned IDE, IND, CW, Accessory Classification Request, or marketing submission (i.e., PMA, HDE, De Novo request, 510(k), Dual, BLA). Some examples of common review topics are biocompatibility, bench testing, cybersecurity, etc. See **Appendix 2** for examples of specific questions within review topics. A Pre-Sub is appropriate when FDA's feedback on specific questions would help guide product development and/or submission preparation, but is not intended to be a pre-review of an intended submission or a pre-review of data to be provided in a submission.

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[2] 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/media/102699/download

[3] See 168 CONG. REC. S5194-S5203 (daily ed. September 28, 2022) (Food and Drug Administration User Fee Reauthorization), also available at https://www.fda.gov/media/158308/download

[4] For the purposes of this guidance document, manufacturers or other parties who submit a Q-Sub, IDE, IND, CW, Accessory Classification Request, or marketing submission to the Agency are referred to as submitters.

The program is entirely voluntary on the part of the submitter. However, early interaction with FDA on planned non-clinical 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 efficient and 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,[5] 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 a favorable decision in 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.

Pre-Subs can be useful to obtain FDA feedback on a wide variety of future submission types, including other Q-Submission types that you intend to submit requesting an FDA decision. One example is an Accessory Classification Request,[6] which is another type of Q-Submission discussed in Section II.F. Accessory Classification Requests are not Pre-Subs, however, a Pre-Sub can be submitted prior to a formal Accessory Classification Request to help guide product development or request feedback about application preparation. When requested, FDA will provide the opportunity for a submitter to meet and discuss the appropriate classification prior to submitting an Accessory Classification Request for an existing accessory type.[7] This meeting would fall within the scope of a Pre-Sub. Submission procedures for the Accessory Classification Request itself are further described in Section II.F.

Pre-Subs are also highly recommended for obtaining feedback on development of Predetermined Change Control Plans (PCCPs) prior to inclusion in a premarket submission. PCCPs are addressed in section 515C of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and allow the manufacturer to make modifications that are within the bounds of the PCCP following FDA authorization of the PCCP.[8] Under section 515C, FDA may under certain circumstances approve or clear a PCCP that describes planned changes that may be made to a device and that would otherwise require a supplemental premarket approval application or a new premarket notification. Specifically, section 515C provides that a supplemental premarket approval application (section 515C(a)) or a new premarket notification (section 515C(b)) is not required for a change to a previously approved or cleared device if the change is consistent with a PCCP that is approved or cleared by FDA. Section 515C also provides that FDA may require that a PCCP include labeling required for safe and effective use of the device as such device changes pursuant to such plan, notification requirements if the device does not function as intended

[5] See FDA's guidance, "The Least Burdensome Provisions: Concept and Principles," and sections 513(i)(1)(D)(i), 513(a)(3)(D)(ii), 515(c)(5)(A), 515(c)(5)(C), 513(a)(3)(D)(iii), 513(i)(1)(D)(ii), and 515(c)(5)(B) of the FD&C Act.
[6] See section 513(f)(6) of the FD&C Act.
[7] See section 513(f)(6)(D)(ii) of the FD&C Act.
[8] Section 3308 of the Food and Drug Omnibus Reform Act of 2022 (FDORA), enacted as part of the Consolidated Appropriations Act, 2023, added section 515C "Predetermined Change Control Plans for Devices" to the FD&C Act (Pub. L. No. 117-328).

pursuant to such plan, and performance requirements for changes made under the plan. FDA encourages the use of a Pre-Sub as it provides an opportunity to work proactively with the FDA in the development of the PCCP, which helps to streamline the premarket review.

B. Submission Issue Requests (SIRs)

A SIR is a request for FDA feedback via written feedback or a meeting on a proposed approach to address issues conveyed in a marketing submission hold letter, a 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 a SIR:

- Additional Information Needed for 510(k)s, De Novo requests, 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).

A SIR is intended to facilitate interaction between FDA and the submitter to quickly address questions about issues identified in these letters so that projects can move forward, and so that submitters are able to fully address outstanding questions and issues in their formal responses. A SIR may be used to discuss a planned approach or strategy for addressing issues identified in an FDA letter. However, a SIR should not be used to request that FDA pre-review an intended formal response to assess adequacy.

Submitters are expected to provide a formal response to any letters received from FDA within the requested timeline regardless of whether a SIR is submitted.

Please note, a SIR is not appropriate for discussing certain letters, such as Not Substantially Equivalent, Withdrawal, and Deletion letters.

A SIR is not necessary for simple requests for clarification of issues in a letter where the involvement of management is not needed (e.g., minor clarification questions or administrative issues that can be addressed by the lead reviewer interactively). A SIR is also not appropriate to discuss issues while a file is under active review.

Refer to Section III.B(4)b of this guidance for additional information on Submission Issue Requests.

C. Study Risk Determinations

A Study Risk Determination is a request for FDA determination for whether a planned medical device clinical investigation is significant risk (SR), nonsignificant risk (NSR), or exempt from most requirements under the IDE regulations (see 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). See 21 CFR 812.2(b)(1). For more information, see FDA's guidance entitled "Information Sheet Guidance For IRBs, Clinical

Investigators, and Sponsors Significant Risk and Nonsignificant Risk Medical Device Studies." 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) and 812.20(a).

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 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.

Informational Meetings can also be used to document FDA and submitter interactions that do not fall within the definition of the other types of Q-Submissions. Additional information on these can be found in Section II.G of this document.

E. PMA Day 100 Meetings

A PMA Day 100 Meeting is a meeting with the FDA that fulfills FDA's obligation,[9] upon written request from the applicant, to meet with the applicant no later than 100 days[10] after the receipt of an original PMA application that has been filed. The purpose of this meeting is to discuss the review status of the application.[11] A PMA Day 100 Meeting can be requested as part of the cover letter of a PMA application or by submitting a separate Q-Submission. If this request is submitted as a separate Q-Submission, it should be submitted no later than 70 days after FDA receipt of a PMA that has been accepted for filing or 70 days after submission of the amendment that enables the PMA to be filed ("filing date"). This timing allows FDA sufficient time to schedule the meeting. Whether requested as part of a cover letter for a PMA application or as a separate Q-Sub, FDA creates a PMA Day 100 Meeting Q-Submission and the applicant receives an acknowledgment letter with the Q-Submission number when the request is received. All discussion regarding the PMA Day 100 Meeting and documentation of the meeting itself should be tracked as part of the Q-Submission. With concurrence of the applicant, a different schedule for the meeting (later than day 100) may be established.[12]

Prior to the meeting, FDA will inform the applicant in writing of any deficiencies in the application that, at that point, have been identified based on an interim review of the entire application and what information is required to correct those deficiencies.[13] This may be in the form of a Major Deficiency letter or, in the case of a decision to "proceed interactively" with the PMA review, it may be a list of minor deficiencies to be resolved interactively during the

[9] See section 515(d)(3)(A)(i) of the FD&C Act.
[10] Unless otherwise specified, in this guidance document, days refers to calendar days.
[11] See section 515(d)(3) of the FD&C Act.
[12] See section 515(d)(3)(B) of the FD&C Act.
[13] See section 515(d)(3)(A)(ii) of the FD&C Act.

remaining PMA review. Note that this written communication of deficiencies will typically occur regardless of whether the applicant requests a PMA Day 100 Meeting.[14] If an applicant requests a PMA Day 100 meeting in the initial submission of the PMA but later decides this meeting is not necessary, the applicant can withdraw the request at any time prior to the meeting.

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 any potential post-approval study requirements.[15]

It should be noted that a PMA Day 100 Meeting may be used to discuss clarifying questions about a Major Deficiency letter or an applicant's preliminary approach for a response. If the applicant would like further discussion of a detailed approach to address the deficiencies provided in a Major Deficiency letter, the applicant should submit a SIR.

The relevant review team members and management will attend the meeting with the applicant, as well as other FDA staff as appropriate.

F. Other Q-Submission Types

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

- Agreement and Determination Meetings as described in FDA's guidance entitled "Early Collaboration Meetings Under the FDA Modernization Act (FDAMA)."
- Submissions associated with the Breakthrough Devices Program as described in FDA's guidance entitled, "Breakthrough Devices Program":
    - Breakthrough Device Designation Request: to request inclusion in the Breakthrough Devices Program according to the criteria specified in

[14] See 168 CONG. REC. S5194-S5203 (daily ed. September 28, 2022) (Food and Drug Administration User Fee Reauthorization), also available at https://www.fda.gov/media/158308/download. See also FDA Guidance Document, "FDA and Industry Actions on Premarket Approval Applications (PMAs): Effect on FDA Review Clock and Goals"

[15] For additional information on post-approval studies, see FDA Guidance Document, "Procedures for Handling Post-Approval Studies Imposed by Premarket Approval Application Order"

section 515B(b) of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

  - Interaction for Designated Breakthrough Device: to request feedback on device development and clinical protocols for devices previously designated as breakthrough.[16]

- Submissions associated with the Safer Technologies Program ("STeP") as described in FDA's guidance entitled, "Safer Technologies Program for Medical Devices":

  - STeP Entrance Request: to request inclusion in the Safer Technologies Program.
  - STeP Interaction Submission: to request feedback on device development and clinical protocols for devices previously included in STeP.[17]

- Accessory Classification Requests as described in FDA's guidance entitled, "Medical Device Accessories – Describing Accessories and Classification Pathways":

  - 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.
  - For a New Accessory Type: to request appropriate classification of an accessory that has not been previously classified under the FD&C Act, cleared for marketing under a 510(k) submission, or approved in a PMA. New Accessory Type classification requests should be submitted together with the premarket submission for the parent device. An Accessory Classification Request will be tracked as a Q-Sub with review and decisions being conducted concurrently with the parent premarket submission.

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

[16] As described in the MDUFA V commitment letter, available at https://www.fda.gov/media/158308/download, certain interactions for designated breakthrough devices are counted as Pre-Subs for MDUFA reporting purposes. However, these interactions have their own process as described in FDA's guidance, "Breakthrough Devices Program." Furthermore, the following requests for feedback for Breakthrough designated devices and device-led combination products are considered accepted for review upon receipt: sprint discussions, requests for review of a data development plan, and requests for review of a clinical protocol agreement.

[17] As described in the MDUFA V commitment letter, available at https://www.fda.gov/media/158308/download, certain STeP interaction submissions are counted as Pre-Subs for MDUFA reporting purposes. However, these interactions have their own process as described in FDA's guidance, "Safer Technologies Program for Medical Devices." Furthermore, the following requests for feedback for devices and device-led combination products included in STeP are considered accepted for review upon receipt: sprint discussions and requests for review of a data development plan.

development and review process, FDA may create additional Q-Sub types that follow the same general principles and processes outlined in this guidance document.

G. Other Uses of the Q-Submission Program

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-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 mechanism is currently used for tracking include:

- Request for FDA feedback on specific questions or cross-cutting policy matters (e.g., submission strategies unrelated to a specific premarket submission, non-clinical testing strategies from third party testing labs) from stakeholders such as industry, other government agencies, non-profits, trade organizations and professional societies. Note that a submission is not necessary for FDA to meet with these groups, but FDA is open to receiving them, should organizations voluntarily submit information in advance of the meeting for FDA's substantive review.[18]

- 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").

- Request for FDA feedback on design elements of a device clinical study that do not fall within the scope of a Pre-Submission, and therefore would not be eligible for discussion under a Pre-Sub. These requests could include requests regarding study design for an NSR or IDE exempt study for which the results are not intended to support a future IDE or marketing submission.

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

- Requests for FDA feedback related to certain device quality and compliance matters. For example, an Informational Meeting Q-Sub could be used to seek feedback during product development or during early stages of establishing a Quality System.

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

[18] For these types of meetings with CBER staff, see https://www.fda.gov/about-fda/about-center-biologics-evaluation-and-research-cber/contacts-center-biologics-evaluation-research-cber#indcont

H. Interactions Not Within the Q-Submission Program

There are several other mechanisms, outside the scope of the Q-Sub Program, through which industry may obtain feedback from FDA. Some require or should have another type of formal submission, while some can be addressed using informal interactions.

Some examples of interactions outside the scope of the Q-Sub Program that may be appropriate for informal interactions (i.e., do not involve a formal submission and may be handled via email or telephone call) include, but are not limited to, the following:

- Administrative questions, or questions about the submission process (e.g., FDA review timelines, when to respond to a deficiency letter).

- Teleconferences or emails with FDA staff (e.g., with the lead reviewer or Regulatory Project Manager (RPM)[19]) discussing general FDA policy, procedures, or simple review clarification questions.

- Interactive review of issues identified while an IDE, IND, or marketing submission is under active FDA review, as described in FDA's guidance entitled "Types of Communication During the Review of Medical Device Submissions."

- Questions that can be readily answered based on an FDA reviewer's experience and knowledge that do not require additional background information, in-depth review, or other FDA staff involvement.

  The following is an example of a question that could be discussed informally:
  - We plan to market a facet screw that has an intended use and design characteristics within the scope of the safety and performance guidance for facet screws (Facet Screw Systems - Performance Criteria for Safety and Performance Based Pathway). If our device falls entirely within the scope of that guidance with no added features, is there any additional testing we should be aware of?

- Requests for clarification on device-specific guidance documents or voluntary consensus standards that are not related to a specific device in development.

- Requests for feedback from FDA via other resources including, but not limited to CDRH Device Advice website,[20] CDRH's Division of Industry and Consumer Education (DICE),[21] or CBER's Manufacturers Assistance and Technical Training Branch.[22]

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[19] 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.
[20] CDRH Device Advice, https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance
[21] You may contact DICE by email at DICE@fda.hhs.gov or by telephone: 1-800-638-2041 or 301-796-7100.
[22] CBER's Manufacturers Assistance and Technical Training Branch may be contacted by email at industry.biologics@fda.gov

Some examples of interactions outside the scope of the Q-Sub Program that may involve another type of formal submission include, but are not limited to, the following:

- Requests for appeal meetings made to CDRH, which are described in FDA's guidance entitled "Center for Devices and Radiological Health (CDRH) Appeals Processes," or to CBER, which are described in FDA documents entitled "Formal Dispute Resolution: Sponsor Appeals Above the Division Level" and CBER SOPP 8005: Formal Dispute Resolution Process.

- Requests for Designation (RFD) or Pre-RFDs, which are submitted to the Office of Combination Products (OCP) when the classification of a medical product as a drug, device, biological product, or combination product, or the product's Center assignment (or both), is unclear or in dispute.[23] Procedures for these processes can be found in FDA's guidances entitled, "How to Write a Request for Designation (RFD)" and "How to Prepare a Pre-Request for Designation (Pre-RFD)." Such classification and assignment information should not be solicited via a 513(g) Request for Information (see below).

- Section 513(g) Requests for Information, which provide a means to obtain information 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 a 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. Additional information regarding 513(g) Requests for Information, can be found in the guidance entitled, "FDA and Industry Procedures for Section 513(g) Requests for Information under the Federal Food, Drug, and Cosmetic Act."

- Requests for Emergency Use Authorizations (EUAs) or requests for feedback about EUA submissions and the EUA process.[24] There is a separate pre-EUA process that should be utilized for discussions about EUAs, which is distinct from the Pre-Submission process. Additional information regarding EUAs and Pre-EUAs can be found in the guidance entitled "Emergency Use Authorization of Medical Products and Related Authorities."

- Total Product Life Cycle (TPLC) Advisory Program (TAP) Pilot interactions. Interactions under the TAP Pilot are not counted as Pre-Subs for MDUFA reporting purposes. Additional information regarding the TAP Pilot can be found on FDA's webpage entitled, "Total Product Life Cycle Advisory Program (TAP)."

If submitters are unsure if a request should be submitted under the Q-Sub Program, we recommend contacting the review division or OPEQ Submission Support (OPEQSubmissionSupport@fda.hhs.gov) to discuss the best pathway for the request.

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[23] Additional information on how combination products are assigned a lead Center for their premarket review and their regulation is available on OCP's webpage (https://www.fda.gov/combination-products). See also FDA Guidance, "Classification of Products as Drugs and Devices and Additional Product Classification Issues."

[24] EUA requests are submitted when requesting emergency use authorization of certain medical products under section 564 of the FD&C Act.

III. Q-Submission Program

The term "Q-Submission" or "Q-Sub" refers to the system used to track the collection of interactions described in Section II.A-G 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, Accessory Classification Request, or CW. Q-Subs can serve as helpful tools in the premarket submission process and FDA reviewers are encouraged to work interactively[25] with submitters while the Q-Sub is under review to maximize the benefits of this process. 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. If a submitter intends to submit more than one Q-Sub to request discussion and/or feedback on various topics for the same device, we suggest that the initial Q-Sub contain an overview of the expected submissions, including general time frames, if known. When submitting more than one Q-Sub for the same product, the order of the submissions should be carefully considered. There may be dependencies in the review of the Q-Subs that make it beneficial to submit and receive feedback on one Q-Sub before initiating another. The intent is for FDA and the submitter to focus on the submitter's current priority. Limiting the content and number of topics in a single Q-Sub allows FDA to focus on the submitter's current priority. Once that priority is addressed, Q-Sub supplements can be used to discuss additional topics related to the same device. Further, significant challenges exist regarding the review of multiple Q-subs on the same device simultaneously. For example, during the review of related Q-Subs submitted at the same time, it may be evident that feedback provided in one Q-Sub might influence the feedback that should be provided in the other Q-Sub, which could make it difficult to provide a thorough response. As such, for any given device, we recommend only one Q-Sub 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.

FDA will keep the existence of Q-Subs confidential, subject to the confidentiality provisions of the FD&C Act, FDA's regulations covering information disclosure, and the Freedom of Information Act (FOIA) (5 U.S.C. § 552). Additional information about confidentiality of meeting information can be found below in Section III.B(3).

[25] See FDA Guidance Document, "Types of Communication During the Review of Medical Device Submissions."

A. General Q-Submission Considerations

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

Many Q-Subs are followed by marketing submissions, IDEs, INDs, CWs, Accessory Classification Requests, 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 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, in accordance with that center's corresponding processes. Accordingly, Q-Submissions should only be submitted for device-led combination products assigned to CDRH or CBER. If the classification or center assignment for a medical product is unclear or in dispute, the submitter should submit an RFD or Pre-RFD to OCP,[26] and then submit their meeting request to the center determined to be the lead center. If a Q-Sub is submitted to the wrong FDA Center, it will be closed and the submitter will be informed that they should resubmit to the correct FDA Center. Proactively submitting an RFD often saves the submitter time by ensuring that the Q-Sub is sent to the correct FDA Center. If CDRH or CBER receives a Q-Sub for a combination product as the lead center for the product, the center's staff intends to notify the other center(s) involved in the 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. When Q-Subs for combination products are submitted, FDA intends to initiate the same review process for the Q-Sub as for single-entity devices. Meetings and/or requests for written feedback may take longer to schedule and/or to address in writing due to factors such as the increased number of Agency staff involved and other regulatory complexities that can be associated with combination products. However, for Pre-Subs discussing combination products, FDA intends to follow the Pre-Sub timeframes described in Section III.B(4). For products that are combination products, the submitter is responsible for identifying

[26] Additional information on how to submit an RFD or Pre-RFD to OCP is available at: https://www.fda.gov/combination-products/rfd-process

it as such in the submission.[27] FDA recommends this information be provided in the cover letter. Where submitters have determined they would like input from the OCP, they may also submit a copy of the cover letter to OCP.[28]

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

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

- *Contact Information.* Company name, address, and contact person(s) including title(s), phone number(s), fax number(s), and email address(es). Note that full 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 each submission.

- *Method of Feedback.* If a Q-Sub includes an option for the method of feedback, it should clearly indicate what type of feedback is being requested. Pre-Submissions offer written feedback only or written feedback followed by a meeting, and SIRs offer either written feedback or a meeting. To ensure feedback is provided and meetings are scheduled in a timely manner, it is important that this is clearly specified in the submission.

- *Meeting Information.* If a Q-Sub type includes the option for a meeting (e.g., a Pre-Sub, SIR, or Informational Meeting request), and a meeting is being requested, the Q-Sub should indicate the following to facilitate scheduling:
    i. A draft agenda proposing the topics to be presented and the estimated time for each agenda item, to the extent possible pending FDA feedback;
    ii. The meeting format being requested (see Section III.B(3)a. below);
    iii. Three (3) or more preferred dates and times when the submitter is available to meet.
        a) While the submitter should propose dates that suit the submitter's 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 FDA is not able to accommodate the requested dates, the submitter will be offered alternative dates within an appropriate timeframe. Refer to the timelines for Pre-Subs (see Section III.B(4)a.2 below), SIRs (see Section

[27] See section 503(g)(8)(C)(v)(I) of the FD&C Act.
[28] The following website contains contact information for OCP: https://www.fda.gov/about-fda/office-special-medical-programs/office-combination-products

III.B(4)b.2 below), and Informational Meetings (see Section III.B(4)d.2 below) when 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 all of the attendees have not yet been identified, the submitter should indicate the type of subject matter experts they plan to invite (see Section III.B(3)b. below).
    b) FDA recommends that submitters 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).

To obtain meaningful feedback from FDA, the following should be easily identified within the body of 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. In addition to a description of the general device, it is important for FDA to have a clear understanding of the specific parts of the device being discussed in the Q-Sub and any device technology relevant to the topic of the Q-Sub.

- *Proposed Indications for Use or Intended Use*. Including a description of the disease(s) or condition(s) the device is intended to diagnose, treat, prevent, cure or mitigate, or the structure or function of the body the device is intended to affect, and a description of the patient population for which the device is intended. Depending on the topic being discussed in the Q-Sub, this information can impact the feedback provided. Therefore, this information is important to include so that FDA can provide accurate feedback.

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

Q-subs are subject to eCopy requirements under section 745A(b) of the FD&C Act. There is also a voluntary electronic Submission Template and Resource (eSTAR) for Pre-Subs (PreSTAR)

available on FDA's website.[29] For more information on eCopy and the submission process, refer to https://www.fda.gov/medical-devices/how-study-and-market-your-device/ecopy-program-medical-device-submissions, including the guidance entitled "eCopy Program for Medical Device Submissions." We recommend that the submission include the CDRH Premarket Review Submission Cover Sheet[30] for eCopy submissions made to CDRH or CBER to facilitate correct login and timely routing to the appropriate review group.

If submitting to CDRH, we recommend submission packages be submitted electronically via the CDRH Portal, previously known as the CDRH Customer Collaboration Portal, as discussed in the following website: https://www.fda.gov/medical-devices/industry-medical-devices/send-and-track-medical-device-premarket-submissions-online-cdrh-portal. Once submitted via the CDRH Portal, the Q-Sub will be received by the CDRH Document Control Center (DCC). Alternatively, submission packages may be mailed to the CDRH DCC. The current mailing address for CDRH's DCC is provided on the eCopy Program for Medical Device Submissions webpage at https://www.fda.gov/medical-devices/how-study-and-market-your-device/ecopy-program-medical-device-submissions.

For products regulated by CBER, we recommend that submission packages be submitted electronically through the FDA Electronic Submission Gateway. Alternatively, they can be submitted through the CBER submission email inbox (150MB max) at CBERDCC_eMailSub@fda.hhs.gov, or via mail to the CBER DCC. Additional information on the FDA Electronic Submission Gateway and the current mailing address for the CBER DCC can be found at the following website: https://www.fda.gov/about-fda/about-center-biologics-evaluation-and-research-cber/regulatory-submissions-electronic-and-paper.

The FDA review clock starts when a submission with a valid eCopy or an eSTAR submission is received; however, for Q-Subs that utilize an acceptance review or technical screening, if a file is placed on hold, the review clock will begin upon receipt of the amendment that is accepted. For submissions using eSTAR, a submission is considered accepted once it has passed technical screening.

(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.

[29] eSTAR is the only type of electronic submission template that is currently available to facilitate the preparation of certain Q-Submissions as eSubmissions. For simplicity, the electronic submission created with this electronic submission template is often referred to as an eSTAR throughout this guidance. The eSTAR for Pre-Subs is also referred to as PreSTAR. FDA's website regarding the eSTAR program, available at https://www.fda.gov/medical-devices/how-study-and-market-your-device/voluntary-estar-program, provides current information regarding the eSTAR program for CDRH and CBER. See also FDA's guidance "Providing Regulatory Submissions for Medical Devices in Electronic Format – Submissions Under Section 745A(b) of the Federal Food, Drug, and Cosmetic Act"

[30] See Form 3514, https://www.fda.gov/media/72421/download

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 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 DCC. Any future communications regarding that 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. Q-Subs submitted to CBER will instead be assigned a number starting with 'BQ'. After the CBER DCC processes the Q-Sub, it will be forwarded to the appropriate Product Office for additional processing and review. The submitter will be contacted by the RPM who will provide a BQ number and who will be the contact for all additional communications.

- *Supplement*. A Q-Sub supplement is any new request for feedback and/or a meeting about the same device with the same or similar indications for use as an original Q-Sub that already exists. For example, it may be appropriate to initially request an Informational Meeting to familiarize the review team with the new device design, then submit a Pre-Sub to request feedback on non-clinical testing, then later submit a Study Risk Determination Q-Sub for the pivotal clinical study, all for the same device with the same 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 a change in contact information, such as submitter organization or correspondent (e.g., consultant) organization is needed, the submitter should submit a Q-Sub amendment to the original clearly stating the change. Note that if a change to the submitter is needed, the Q-Sub submitter of record (the submitter recorded in our system) should provide a letter authorizing the change in submitter. If a change to the submitter is not needed, but the submitter wants 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 the submitter would like to use

a different correspondent contact person for a given supplement, they do not have to submit an amendment; they can indicate the appropriate correspondent contact person when that supplement is submitted.

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, non-clinical, or analytical studies related to an IDE, IND, CW, Accessory Classification Request, or marketing submission. During a Q-Sub meeting, FDA will be prepared to discuss the contents of the Q-Sub as well as the written feedback the Agency provided for that Q-Sub (if applicable). Submitters should not expect FDA to comment on new information provided by the submitter between receiving FDA written feedback and holding the meeting or during the meeting, as there is generally insufficient time for FDA to thoroughly review the information. 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 should provide draft slides to FDA electronically (e.g., in Microsoft PowerPoint or PDF) at least two (2) days before the meeting. This will allow adequate time to distribute the presentation to all participating FDA staff.

Submitters that request a meeting should be aware that all meeting minutes and materials are subject to disclosure review pursuant to the Freedom of Information Act (FOIA), 5 U.S.C. 552. Meeting minutes and materials, like all Agency records, may be the subject of a FOIA request and unless information in the records being requested is exempt from release under the FOIA, it will be released to requesters.

a. Meeting Format

If desired, FDA is available to meet to discuss our feedback. It is typically most efficient to meet virtually (i.e., videoconference or teleconference), as these meetings are easier to schedule in a timely fashion. Upon request, in-person meetings may be available, and we recommend that the submitter contact the lead reviewer if there is interest in having such a meeting. An in-person meeting can include virtual attendees. For an in-person meeting, the submitter should inform the lead reviewer or meeting coordinator if any specific equipment will be needed or if there will be virtual attendees. The meeting coordinator or lead reviewer will reserve the room and arrange for any audiovisual equipment that may have been requested. Please note visitors are not allowed access to any FDA/HHS information technology systems. This includes attaching USB cables, flash drives and any network-connected FDA/HHS equipment. If internet access is needed for the meeting, visitors should make this request at least five (5) days prior to the meeting.

Meetings will normally be limited to one (1) hour. In our experience, this is the optimal amount of time for discussing selected Q-Sub topics. If more than an hour is needed, the scope of the Q-

Sub may be too large, and we recommend that the submitter consider limiting the scope of the submission to allow a more focused discussion that may yield more useful feedback.

b. Meeting Attendees

FDA will always attempt to ensure the appropriate FDA staff is present at Q-Sub meetings. 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. The submitter 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 a submitter wishes to address. For example, if statistical issues are included in the focused questions, it is appropriate to suggest that an FDA statistician attend. In addition, if the submitter wishes to have additional management or policy staff (e.g. CDRH's Digital Health Center of Excellence staff or OPEQ's ORP staff) included in a meeting they can make this request.

All non-U.S. citizens attending a meeting in an FDA facility are subject to additional security screening. If non-U.S. citizens plan to attend, submitters 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.

Submitters are invited and encouraged to include any additional outside individuals (e.g., Centers for Medicare & Medicaid Services (CMS) staff, private payors, NIH grant reviewers) in Q-Sub meetings, as appropriate. Including additional representatives may be helpful in maintaining transparency, efficiencies, and consistency among the various stakeholders for the device. As patient access to many novel medical devices may be limited due to uncertainties regarding insurance coverage and reimbursement, early communication with payors may enable a medical device developer to learn the specifics of payor's data/evidentiary needs and to incorporate capturing that data within the same clinical trial(s) being designed to support FDA marketing authorization. Submitters may request payor feedback, or payor attendance at a Q-Sub meeting, through the Early Payor Feedback Program.[31] Submitters are responsible for scheduling and coordinating the appropriate invitations with payors and any other external stakeholders that they wish to include in a Q-Sub meeting and defining their roles and/or participation during the meeting.

c. Meeting Minutes

As stated in the MDUFA V commitment letter, the submitter is responsible for drafting meeting minutes for all Pre-Sub meetings and submitting them to FDA as an amendment to the Pre-Sub within 15 days of the meeting.[32] Submitters should draft meeting minutes and submit them to FDA using this same timeframe and process for all Q-Sub meetings. The meeting minutes should be an accurate reflection of the meeting discussion. Rather than being a transcript of the meeting,

[31] For more information about the Early Payor Feedback Program, see the following website: https://www.fda.gov/about-fda/cdrh-innovation/medical-device-coverage-initiatives-connecting-payors-payor-communication-task-force

[32] See 168 CONG. REC. S5194-S5203 (daily ed. September 28, 2022) (Food and Drug Administration User Fee Reauthorization), also available at https://www.fda.gov/media/158308/download

the minutes should summarize the meeting discussion, document how substantial or complex issues were resolved, and include agreements and any action items. It should not assign statements to individuals, but to the submitter or FDA generally. Additional information or follow-up items that were not part of the meeting discussion should not be included in the meeting minutes. We have included an example format of meeting minutes in **Appendix 3** for reference.

The submitter should have a member of their 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 should affirmatively state that they will draft minutes and provide them to FDA within 15 days. Consistent with 21 CFR 10.65(e), the official record of this meeting will be the FDA-generated minutes. Attendees should not make audio or visual recordings of discussions at meetings described in this guidance.

To submit meeting minutes, a submitter must use eCopy format and send through the appropriate DCC (via mail or electronically, as specified in Section III.B(1) above). If slides were presented, the actual version used in the meeting 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. In addition to the official meeting minutes submitted to the DCC, the submitter is encouraged to submit an identical version of the meeting minutes in a format that facilitates editing and commenting (e.g., Microsoft Word) under the miscellaneous files section of the eCopy package (see FDA Guidance Document "eCopy Program for Medical Device Submissions," Attachment D.2).

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 the draft minutes, FDA intends to email the revised version of the minutes to the submitter 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 days after FDA's edits are received, unless the submitter indicates to FDA that there is a disagreement with how a significant issue or action item has been documented. If such a disagreement exists, the submitter should submit an amendment to the Q-Sub through the appropriate DCC (via mail or electronically, as specified in Section III.B(1) above), labeled as a "meeting minutes disagreement." In the case of a disagreement, FDA will set up a mutually agreeable time for a teleconference to discuss that issue, in a timely manner. At the conclusion of that teleconference, within 15 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. Any differences of opinion regarding regulatory or scientific advice can be addressed by submitting an additional Q-Sub supplement 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. The Q-Sub types, corresponding feedback mechanisms, and timelines

that FDA strives to meet are summarized in Table 1. For Q-Sub types outside the scope of this guidance, please find this information in their corresponding guidance documents.

Table 1 – Q-Sub types and corresponding feedback mechanisms and timelines

Q-Sub Type	Method of Feedback	Timeframe for Sending Feedback or Scheduling Meeting (from receipt of Q-Sub unless otherwise noted)
Pre-Submission^	Meeting with written feedback provided in advance	Written Feedback: 70 days or 5 days prior to scheduled meeting, whichever is sooner Meeting: Date based on mutual agreement (typically day 70-75)
	Written Feedback Only	70 days
Submission Issue Request (SIR)	Meeting **or** Written Feedback	If SIR is received **within 60 days** of an applicable FDA letter: # 21 days as resources permit
		If SIR is received **more than 60 days** after an applicable FDA letter: # 70 days as resources permit
Study Risk Determination	Formal Letter	90 days
Informational Meeting*	Meeting	90 days
PMA Day 100 Meeting	Meeting+	100 days from the PMA filing date

^ Section II.A of the MDUFA V commitment letter describes goals for achieving Pre-Sub timelines.
* When used to track requests that do not meet the definition of a Q-Sub type, Informational Meeting timeframe and feedback mechanism can vary. Typically, informational meetings do not include FDA feedback.
+ Prior to the Day 100 Meeting, FDA provides a description of any deficiencies that, at that point, have been identified. Such feedback may be provided in the form of a Major Deficiency letter or via deficiencies identified in a "proceed interactively" email.[33]
# As discussed in Section II.B of this guidance, the following FDA letters are applicable: marketing submission hold letters, CW hold letters, IDE Letters, and IND Clinical Hold letters.

a. Pre-Submission

1) Additional Recommended Submission Contents

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

[33] For more information, see the FDA guidance "FDA and Industry Actions on Premarket Approval Applications (PMAs): Effect on FDA Review Clock and Goals"

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

- *Background Information.* FDA recommends that sufficient background information and supporting documents be included to allow FDA to develop feedback for the Pre-Sub questions posed. 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 feedback is requested. It may also be helpful to include how the submitter addressed, or plans to address, relevant guidance documents, regulations, special controls, or other applicable sources for the specific device or submission type.

  While the importance of a complete background package cannot be overstated, it should also be noted that submission of extraneous information can be counterproductive. FDA recommends that a submission be targeted and focused. If significant background information is needed to provide appropriate context, it is helpful if it is indicated which background information is relevant to the specific questions or topics for discussion.

- *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 non-clinical and clinical testing protocols or data needed to support the submission) to allow FDA and the submitter to focus their efforts on issues most relevant to moving a project forward. A submitter may wish to describe their perspective on the questions provided to FDA to inform FDA's review.

  FDA recommends carefully considering the number of topics and the 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, and to enable focused meetings. In general, FDA has found it difficult to address more than 3-4 substantial topics in a single Pre-Sub. A substantial topic involves a focused area of expertise. Examples of substantial topics include, but are not limited to, benchtop performance testing, biocompatibility, an animal study, a PCCP, software/firmware (including specific questions that relate to software as a medical device (SaMD)[34]), sterility and shelf life, clinical study endpoints, and statistical analysis plan. Therefore, FDA recommends that the submitter identify no more than 3-4 substantial topics as this facilitates more productive meetings and results in more effective conversations and feedback. Additional straightforward questions (e.g., administrative topics) may be appropriate if they can be addressed without in-depth review and do not introduce new significant topics. If an excessive number of topics are included in the submission, FDA may contact the submitter to discuss which topics the submitter would like to prioritize. In some cases, FDA may suggest discussing the lower priority topics in subsequent Pre-Subs.

[34] For additional information regarding SaMD, see the following webpage: https://www.fda.gov/medical-devices/digital-health-center-excellence/software-medical-device-samd

Furthermore, FDA has found that Pre-Subs with too many questions do not result in as productive discussions or feedback. Increasing the number of questions in a submission can also increase the likelihood that FDA feedback will impact the other questions being asked. Providing feedback to questions that are dependent on each other can lead to difficulty in providing clear feedback to each question, and FDA may not be able to provide productive feedback on the dependent questions. Based on this experience, FDA recommends the submitter limit the size of a Pre-Sub so that FDA is able to conduct a thorough review and provide valuable feedback. The most effective Pre-Subs typically have no more than 7-10 questions (including sub-questions). These questions are usually divided between no more than four substantial topics (for example, the first topic with 3 questions, the second topic with 3 questions, the third topic with 2 questions, and the fourth topic with 2 questions).

If there are a large number of questions on a single topic, it may be beneficial to submit a Pre-Sub with a single topic and to include multiple questions on that specific topic. This strategy would allow the submitter to identify the topics and specific areas of feedback that are their current priority so that FDA can focus on these high priority topics and provide the most useful feedback.

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

- *Study Protocols*
  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.

  For more productive feedback, we recommend that the submitter include specific questions about their protocol. Without directed questions, FDA's feedback may be more general in nature and not provide adequate specifics on the area of interest.

  If the Pre-Sub is for a nonsignificant risk device study, IDE exempt device study, 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 not appropriate for a Pre-Sub. 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*

In a Pre-Sub, FDA may be able to provide limited feedback regarding potential regulatory strategy and approach. For example, a request for feedback regarding whether a device cleared under a 510(k) or for which a De Novo request was granted has the potential to serve as a predicate for a proposed device would be appropriate for a Pre-Sub. In contrast, a request for information about the classification and regulatory requirements applicable to a device is not within the scope of a Pre-Sub. Such requests are governed by section 513(g) and should be submitted as a 513(g) Request for Information.[35] See Section II.H 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.

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

- *Additional Considerations.* When preparing a Pre-Sub, FDA recommends that the following information be considered:
  - If there is a device-specific guidance or other FDA resources applicable to the device, submitters should review them prior to submission of a Pre-Sub.
  - Submitters should consider whether feedback on one question may impact the answer to another. For example:
    - Feedback regarding performance testing will likely be dependent on the proposed indications for use/intended use and planned regulatory pathway. It may be premature to discuss performance testing plans without a well-defined indication for use/intended use and without determining the planned regulatory pathway.
    - If asking about a clinical study protocol, submitters should have already decided upon the planned indications for use and know what other non-clinical data they are planning to provide to support a premarket submission.
    - If the submitter is still in design stage and expects to make technological changes to the device, it may be premature to ask about performance testing.

  In these cases, it may be appropriate to limit topics to the ones that are the highest priority and will inform questions on other issues, obtain FDA feedback, and then submit additional topics in a subsequent Pre-Sub(s). Otherwise, FDA may not be able to provide productive feedback on the dependent questions.

2) Review Process

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

[35] See FDA guidance document "FDA and Industry Procedures for Section 513(g) Requests for Information under the Federal Food, Drug, and Cosmetic Act"

- *Acceptance Review/Technical Screening*[36]. Within 15 days of the review clock starting, FDA staff will conduct an acceptance review using the Acceptance Checklist (see **Appendix 1 – Pre-Submission (Pre-Sub) Acceptance Checklist**) or a technical screening for an eSubmission submitted using eSTAR.[37] When completed, the submitter will receive notification regarding whether or not the submission has been accepted for review, or passed the technical screening, as well as the contact information for the lead reviewer or the RPM. If a Pre-Sub requesting a meeting is accepted, or passes technical screening, this notification will also either confirm one of the submitter's requested meeting dates or provide two alternative meeting dates prior to day 75 from receipt of the accepted submission.

  If the acceptance review or technical screening determines that the request does not qualify as a Pre-Submission or the submission is not complete, FDA staff will obtain concurrence from management of the decision to place the submission on a Refuse to Accept (RTA) hold or a technical screening hold. The submitter will receive notification of this decision with the reasons for the hold. The submitter may respond to an RTA notification or technical screening hold by submitting additional information to the DCC (via mail or electronically, as specified in Section III.B(1) above), which will be logged in as an amendment to the Q-Sub. Upon receipt of the newly submitted information, the review clock will restart at day 0, and FDA staff will conduct the acceptance review or technical screening again, following the same procedure, within the first 15 days of the restarted review clock. The subsequent acceptance review or technical screening will assess whether the new information makes the submission complete.

- *Scheduling of Meeting.* FDA will attempt to schedule a meeting on one of the submitter's requested meeting dates, if feasible. Meeting dates between 70-75 days following FDA receipt of the 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 receipt of accepted submission or a submission that has passed technical screening (i.e., the review clock start date). FDA intends to reach agreement with the submitter regarding a meeting date within 30 days from the review clock start date. For all requests for meetings that do not have an agreed upon meeting date scheduled by 30 days from the review clock start date, 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 and will include: written responses to the submitter questions; FDA's suggestions for additional topics for the meeting, if applicable; or, a combination of both. FDA intends to follow the timeline below for providing feedback to a Pre-Sub.

[36] Certain requests for feedback available to Breakthrough-designated products and/or products included in the Safer Technologies Program (STeP), which are counted as Pre-Subs for MDUFA reporting purposes, are considered accepted for review upon receipt. See section II.F.

[37] For eSubmissions submitted using eSTAR, FDA intends to employ a technical screening process. A technical screening is a process for verifying that eSTAR responses accurately describe the device(s) and that there is at least one relevant attachment per each applicable attachment-type question. Given that an eSubmission properly prepared with an eSTAR should represent a complete submission as described in the Pre-Sub Acceptance Checklist, the technical screening process ensures that the content within the Pre-Sub Acceptance Checklist has been submitted.

- Pre-Sub Written Feedback: If no meeting is requested, written feedback will be provided within 70 calendar days from the review clock start date 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 the review clock start date. If all the submitter's questions are addressed to the submitter's satisfaction through the written feedback, 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 along with the written feedback will constitute the official record of the Agency's feedback. The process and timeline for preparing and finalizing meeting minutes are described in Section III.B(3)c of this guidance.

FDA should not be expected 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, as FDA generally does not have sufficient time to conduct a thorough review of this information. Any information that necessitates additional FDA review should be submitted as a supplement to the Pre-Sub or in the eventual premarket submission. It is, however, appropriate to narrow the 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, CW, Accessory Classification Request, or marketing submission is consistent with that provided in the Pre-Sub, and that new information 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 feedback will be limited to situations in which FDA concludes that the feedback given previously does not adequately address important new issues that have emerged since the time of the Pre-Sub, and that are materially relevant to a determination of a reasonable assurance of safety and/or effectiveness, substantial equivalence, or other relevant regulatory decision. 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 addition, FDA may modify feedback if the submitter makes significant changes to the intended use of the device, device technology, or labeling, or provides new information about the device that alters the safety and/or effectiveness. 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, consistent with applicable SOPs.[38] Further, FDA intends to

[38] The CDRH SOP: Decision Authority for Additional or Changed Data Needs for Premarket Submissions should be followed: https://www.fda.gov/about-fda/cdrh-reports/sop-decision-authority-additional-or-changed-data-needs-premarket-submissions

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

Because clinical practice, testing methods, and medical device technology are constantly evolving, we recommend that if more than one (1) year has passed since previous FDA feedback was received (via Q-Sub or other formal feedback methods) on significant study design topics, and the study has not been initiated, submitters should contact the review division to confirm that our previous advice is still applicable. This can be accomplished through a phone call or email to the lead reviewer, RPM, or appropriate level manager (e.g., Assistant Director). If further discussion or review are needed, then the lead reviewer or RPM may recommend submitting a new Pre-Sub.

When reviewing a Pre-Sub and providing feedback, FDA generally focuses our review on the information relevant to the specific questions and provides specific feedback to address them. If additional information is included, FDA may not need to review this information in order to provide the requested feedback. FDA intends to use the provided information to address the questions included in the Pre-Sub, but does not intend to discuss topics that are unrelated to the Pre-Sub questions and are not discussed in the submission. If FDA's feedback does not mention a topic that is outside the scope of the Pre-Sub questions, additional information on that topic may still be needed in future submissions when that topic is subject to review (even if that information previously was provided).

b. Submission Issue Request (SIR)

1) Additional Recommended Submission Contents

In addition to the general information that should be included in any Q-Sub type to ensure appropriate login and submission tracking (see Section III.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 needed to support the submission), 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 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: either written feedback or a meeting

(not both). If a submitter chooses a SIR meeting, written feedback will not be provided. The meeting minutes will serve as the record of the discussion and should be drafted by the submitter (see Section III.B(3)c).

2) Review Process

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

- *Feedback.* Feedback will be provided either in the form of a written response, or a meeting. In the spirit of the MDUFA Shared Outcome goals for Total Time to Decision, FDA is committed to resolving review issues promptly and will place added emphasis when Industry similarly works expeditiously to address such issues.[39] Accordingly, FDA intends to prioritize review of SIRs submitted within 60 days of the marketing submission hold, IND Clinical Hold, or IDE letter. Timely submission of a SIR allows 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 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 60 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 60 days after FDA's letter, FDA will aim to provide feedback within 70 days, as resources permit.

Submission of, and FDA's response to, a SIR does not change the response due date of an application on hold. Submitters should plan their response timing accordingly. If a meeting is held to provide feedback, the submitter should provide meeting minutes as described in Section III.B(3)c of this guidance.

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 III.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.

[39] See 168 CONG. REC. S5194-S5203 (daily ed. September 28, 2022) (Food and Drug Administration User Fee Reauthorization), also available at https://www.fda.gov/media/158308/download

- *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 Nonsignificant Risk (NSR). The submitter 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 recommended 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 III.B(1)). As Informational Meeting requests may be used for multiple purposes (see Section II), 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.

e. PMA Day 100 Meeting

1) Additional Recommended Submission Contents

In the written request for a PMA Day 100 Meeting, the applicant should specify the type of meeting desired (e.g., in person or virtually), provide a list of persons who will attend for the company, and identify several possible dates for the meeting. After a letter filing the PMA application has been issued, the reviewing division will contact the applicant to set up the meeting if requested. If the PMA Day 100 Meeting request is submitted separately from the PMA cover letter, it should also include the PMA number and the general information that should be included in a cover letter for all Q-Sub types to ensure appropriate login and submission tracking (see Section III.B(1)).

2) Review Process

- *Acceptance Review.* There is no Acceptance review for a PMA Day 100 Meeting.

- *Meeting.* FDA aims to hold a PMA Day 100 Meeting no later than 100 days after the receipt of a PMA application that has been filed. With concurrence of the applicant, a different schedule may be established.

The applicant should draft and provide meeting minutes as described in Section III.B(3)c of this guidance.

After the PMA Day 100 Meeting, FDA will continue to communicate promptly with the applicant on the status of the review and what, if any, additional information has been identified that is required to achieve completion of the review and final action on the application.[40]

[40] See 515(d)(3)(A)(iii) of the FD&C Act

(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 Agreement and Determination Meetings,[41] Breakthrough Device submissions,[42] Accessory Classification Requests,[43] STeP submissions,[44] requests for recognition of publicly accessible genetic variant databases,[45] and CPAMs.[46]

FDA intends to describe policy and procedural information regarding any Q-Sub types that may be created in the future through appropriate mechanisms so that timelines and submission expectations are known.

IV. Paperwork Reduction Act of 1995

This guidance contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520).

The time required to complete this information collection is estimated that an average of 137 hours is required to prepare a Q-Submission. Send comments regarding this burden estimate or suggestions for reducing this burden to:

FDA PRA Staff,
Office of Operations,
Food and Drug Administration,
PRAStaff@fda.hhs.gov

[41] See FDA guidance document "Early Collaboration Meetings Under the FDA Modernization Act (FDAMA)"
[42] See section 515B(c) of the FD&C Act and FDA guidance document "Breakthrough Devices Program"
[43] See FDA guidance document "Medical Device Accessories - Describing Accessories and Classification Pathways"
[44] See FDA guidance document "Safer Technologies Program for Medical Devices"
[45] See FDA guidance document "Use of Public Human Genetic Variant Databases to Support Clinical Validity for Genetic and Genomic-Based In Vitro Diagnostics"
[46] Defined under section 503(g)(2)(A) of the FD&C Act.

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

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

		Yes	No
1	Has the submitter provided a specific purpose or goal for their Pre-Sub?	☐	☐
2	Has the submitter described the device(s) or other product(s) to be discussed in their Pre-Sub?	☐	☐
3	Has the submitter provided specific, focused questions that request FDA feedback?	☐	☐
4	Does the submission indicate that the submitter intends to submit a future IDE, CLIA Waiver by Application, IND, Accessory Classification Request, 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,[47] 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)

[47] FDA considers the following to be marketing submission hold letters or CLIA hold letters:
- Additional Information Needed for 510(k)s, De Novo 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, Accessory Classification Request, 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 request specific feedback on a limited number of focused topics.

For example, questions leading to the most valuable feedback generally:

- 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)
- Have considered and include references 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)
- Clearly articulate a desired outcome including indications for use or labeling statements (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, or to support statements in labeling related to device performance)
- Are in submissions that 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 that ask the review division about the final outcome of an IDE, IND, CW, Accessory Classification Request, or marketing submission, or ask open-ended questions about a study design of a study are, in general, not recommended in a Q-Sub. For example,

- Questions about final outcome such as, "Will an IDE that includes results from the proposed testing be approved?" or "Will this proposal support a determination of substantial equivalence?"
- Questions requesting FDA to design a study or indicate how a submitter should proceed with their clinical study; that is, a question should not ask "What should my clinical study design be?" or open-ended questions such as, "Does FDA have any other feedback on my clinical study?"
- A question should not request a formal regulatory determination such as, "Is my device a Class II medical device to be regulated under CFR 892.2050?" or "Can FDA confirm my device is eligible for a 510(k) or De Novo?"
- In general, a question should 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 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)

The following are examples of questions, provided by review topic category, expected to lead to productive Pre-Sub interactions. Please note that this is not intended to be an exhaustive list of review topic categories.

Regulatory Strategy Questions

- Is the proposed predicate device appropriate if we demonstrate substantial equivalence?
- We would like to obtain FDA's feedback and guidance on pursuing a De Novo request. We are not aware of any predicate devices with this indication with similar technology, but we think our product is moderate to low risk and therefore a De Novo request would be appropriate. Is FDA aware of any additional predicate devices that we should consider? Is FDA aware of any technological concerns that we should consider in our risk assessment?
- Based on the regulatory strategy and discussion of pre-clinical testing provided, does FDA concur that clinical data is likely not needed to support a future 510(k)?

Indications for Use/Intended Use Questions

- Does FDA have any concerns with our proposal to label the described device as over-the-counter?
- Is the proposed definition of drug-resistant hypertension provided in the draft indications for use statement acceptable?
- Is the proposed size range offered for the new device, based on the intended use, appropriate?

Clinical Study Questions

- Is the proposed OUS study adequate to support a future HDE for our device?
- Are the revised clinical study designs, statistical analysis and acceptance criteria included in this Pre-Sub supplement adequate to address FDA's concerns?
- Are the primary and secondary endpoint analyses appropriate for the proposed Indications for Use?

Labeling Questions

- Is the proposed test plan in support of MR Conditional labeling for 1.5T scanners with an exclusion zone between the neck and groin acceptable (i.e., is the test plan consistent with the recommendations of FDA guidance)?
- 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. Is this plan consistent with the current recommendations provided in FDA guidance for the reprocessing of medical devices?

Reprocessing, Sterilization & Shelf Life Questions

- Are the methods described in the Microbiology protocol "Micro-biology Study Protocol" included in Appendix 3 sufficient to demonstrate the sterility of our device?

- Appendix 2 includes an outline of our proposed approach to provide accelerated aging tests conducted to represent 1 year shelf life. Is this approach sufficient for initiation of our planned IDE?
- 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?
- Is our proposal to low level disinfect the cannula device between uses consistent with the recommendations of FDA guidance on the reprocessing of medical devices?

Non-clinical Bench Performance Testing Questions

- Is our provided justification for the proposed worst-case comparison testing acceptable?
- 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.
- Is the approach to use the average of valid measurements of the five replicate measurements acceptable/appropriate?
- 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[48, 49] Questions

- Is the revised GLP Study design sufficient to address potential device risks and support initiation of a pivotal clinical trial?
- Is our alternative approach to an animal study appropriate to support initiation of a pivotal clinical trial?
- Is our proposal to leverage the animal studies already conducted (and described in this submission) adequate to support a future marketing application?
- Does the proposed animal study design 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. Is the largest model dialyzer adequate to be considered the worst-case test article? Is the proposed testing in line with the recommended contact

[48] FDA supports the principles of the "3Rs," to replace, reduce, and/or refine animal use in testing when feasible. We encourage sponsors to consult with us if they wish to use a non-animal testing method they believe is suitable, adequate, validated, and feasible. We will consider if such an alternative method could be assessed for equivalency to an animal test method.

[49] For information on the FDA's recommendations for animal studies intended to evaluate medical devices, see FDA's guidance titled "General Considerations for Animal Studies Intended to Evaluate Medical Devices"

classification and duration [insert classification and duration here] to support our future marketing submission?
- We propose to conduct chemical characterization (described in Appendix 1) in lieu of chronic toxicity testing to support the biocompatibility of our device in a future PMA. Is this approach adequate to allow for collection of sufficient safety data?
- Is our justification for not conducting carcinogenicity studies adequate?
- Is our alternative test method to the material-mediated pyrogenicity testing, which does not use a traditional rabbit model but an in vitro alternative, acceptable?

Software/Firmware Questions

- Is the designation of our software/instrument at a Basic Documentation Level consistent with the recommendations provided in FDA's guidance entitled "Content of Premarket Submissions for Device Software Functions" as part of the upcoming device submission?
- Does FDA recommend any further data validating functional operation of [the emerging technology] for this device beyond that recommended in FDA's guidance entitled "Content of Premarket Submissions for Device Software Functions"? If so, can FDA give us additional guidance on what additional information is recommended?
- The software documentation defined in Section 4.2 of this Pre-Sub for the device was previously reviewed and approved in other PMA supplements (i.e., the PMA supplement will reference previously submitted information). Is it acceptable to omit this information from the planned PMA supplement?
- Our product is a multiple function device product that includes a device software function as well as non-device or "other" functions, as described in the "Multiple Function Device Products: Policy and Considerations" guidance. We would like to present our planned approach to assessing the impact of the other functions on the safety and effectiveness of the subject device function and ask if there is FDA agreement with our approach.

Human Factors Questions

- Is the human factors test protocol, submitted in Attachment 1, adequate to collect safety data to support our future marketing submission?
- Is the attached use-related risk analysis plan adequate? Does the Agency have any additional critical tasks that we should consider?
- Is the proposed test participant recruitment plan for the human factors validation testing appropriate?

Cybersecurity Questions

- Are the attack vectors that have been identified for our product as described in Appendix R acceptable?
- Is the cybersecurity management plan, described in Section 2, sufficient to ensure cybersecurity of our device for our future 510(k) submission? If not, can FDA provide feedback on what additional cybersecurity information is needed?
- Is the proposed risk model adopted for assessing cybersecurity in this device acceptable?
- Is the level of security described appropriate for the risk of the device?

Computational Modeling and Simulation Questions

- In the attached credibility assessment plan, we describe our question of interest for the subject device and propose a context of use (COU) to address the question of interest. Does FDA agree with our proposed computational model COU?
- In the attached credibility assessment plan, we perform a model risk assessment. Does FDA agree with this model risk assessment and our proposed model influence and decision consequence?
- In the attached credibility assessment plan, we perform a prospective adequacy assessment. If our proposed credibility activities are successful, does FDA agree that the plans are adequate to demonstrate that the credibility of our model is commensurate with the assessed model risk?

Appendix 3 – Example of Meeting Minutes

To improve understanding of what FDA expects to see in meeting minutes that submitters provide for Q-Subs, the following example is provided. However, use of this specific format is optional.

As noted above, when the submitter submits their meeting minutes, a copy of the slides you presented at the meeting should also be included.

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
Submitter: Company name
Meeting Date/Time: e.g., January 1, 2014; 2:00 pm
Meeting Format: In-person or Virtual (videoconference 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 necessitate further consideration, as applicable. It is suitable to indicate, for example, "after some discussion, it was decided that the non-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)

Meeting Discussion for Question 1:
(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. We recommend that you 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.)

Guidance History*	Date	Description
Reissued as Level 1 Draft Guidance	March 2024	See Notice of Availability for more information.**
Level 1 Final Guidance	May 2025	See Notice of Availability for more information.**

*This table was implemented, beginning February 2025 and previous guidance history may not be captured in totality.
**The Notice of Availability is accessible via the Search for FDA Guidance Documents webpage.