Guidance for Industry and FDA Staff

Interactive Review for Medical Device Submissions: 510(k)s, Original PMAs, PMA Supplements, Original BLAs, and BLA Supplements

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For questions regarding this document, contact the Premarket Notification (510(k)) Section or the Premarket Approval Section of CDRH at 240-276-4040 or Leonard Wilson of CBER by phone at 301-827-0373 or by email at leonard.wilson@fda.hhs.gov.

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Preface

Public Comment

Written comments and suggestions may be submitted at any time for Agency consideration to the Division of Dockets Management, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD, 20852. Alternatively, electronic comments may be submitted to http://www.fda.gov/dockets/ecomments. Please identify your comments with the docket number listed in the notice of availability that publishes in the *Federal Register* announcing the availability of this guidance document. Comments may not be acted upon by the Agency until the document is next revised or updated.

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Additional copies are available from the Center for Devices and Radiological Health (CDRH) through the Internet at: http://www.fda.gov/cdrh/ode/guidance/1655. You may also send an e-mail request to dsmica@fda.hhs.gov to receive an electronic copy of the guidance document or send a fax request to 240-276-3151 to receive a hard copy. Please use the document number (1655) to identify the guidance document you are requesting.

Additional copies of this guidance document are also available from the Center for Biologics Evaluation and Research (CBER), Office of Communication, Training and Manufacturers Assistance (HFM-40), 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, or by calling 1-800-835-4709 or 301-827-1800, or from the Internet at http://www.fda.gov/cber/guidelines.htm.

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

1. Introduction

The Medical Device User Fee and Modernization Act (MDUFMA) of 2002 amended the Federal Food, Drug, and Cosmetic Act (the Act) to authorize the FDA to collect user fees for premarket reviews of certain device submissions. In return, FDA committed to meeting review performance goals set forth in the letter from the Secretary of Health and Human Services to the Chairman of the Committee on Heath, Education, Labor, and Pensions of the Senate and the Chairman of the Committee on Energy and Commerce of the House of Representatives.[1]

Effective October 1, 2007, Congress reauthorized MDUFMA in the Food and Drug Administration Amendments Act of 2007 (FDAAA). FDAAA authorizes FDA to continue to collect user fees and established the framework for a more aggressive set of performance goals.[2] To meet these new performance goals, both FDA and regulated industry agreed that FDA should implement a formalized interactive review process to encourage and facilitate communication between FDA staff and industry during the review of specific medical device premarket submissions: premarket notification submissions (510(k)s), original premarket approval

[1] Refer to http://www.fda.gov/cdrh/mdufma/pgoals.html for details.

[2] MDUFMA is referred to as the Medical Device User Fee Amendments of 2007 (MDUFA) in Title II of FDAAA. Applicants should note that MDUFMA timeframes remain applicable to medical device submissions filed prior to October 1, 2007. MDUFA timeframes are only applicable to medical device submissions filed on or after October 1, 2007. For the sake of simplicity, the phrase "MDUFA" will be used throughout this document to refer to both sets of timeframes.

applications (PMAs), PMA supplements, original biologics license applications (BLAs), and BLA supplements.[3]

Both FDA and industry believe that an interactive review process for these types of premarket medical device submissions should help facilitate timely completion of the review based on accurate and complete information. Interactive review is intended to facilitate the efficient and timely review and evaluation by FDA of premarket submissions. The interactive review process contemplates increased informal interaction between FDA and applicants, including the exchange of scientific and regulatory information. More specifically, the interactive review process is designed to help accomplish the following:

- improve the interaction between the FDA review staff and the applicants during the review process;
- prevent unnecessary delays in the completion of the review, thus reducing the overall time to market;
- try to ensure that FDA's concerns are clearly communicated to the applicant during the review process, as appropriate;
- minimize the number of review cycles;
- minimize the number of review questions conveyed through formal requests to applicants for additional information; and
- ensure timely responses from applicants.

The purpose of this guidance document is to describe the roles of both FDA and industry (applicants) in an interactive review process for 510(k)s, original PMAs, PMA supplements, original BLAs, and BLA supplements. FDA expects that the interactive review process will enable the agency to make final decisions earlier. FDA intends to periodically assess the interactive review process to determine its success in meeting its objectives.

For the interactive review process to be successful, applicants should provide submissions that are well organized and administratively and scientifically complete. FDA encourages applicants to discuss any major issues with FDA prior to submission to ensure that the content of the submission appropriately addresses regulatory and scientific issues.[4] Although pre-submission interaction is not within the scope of this guidance document, this type of interaction can be helpful in developing a complete submission.[5] FDA encourages applicants to read and consider

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[3] FDA developed this guidance document for direct communication between the agency and industry, but FDA also intends to apply the general concept of interactive review to communication with Accredited Persons that submit third party reviews of 510(k)s.

[4] Although pre-submission interaction is not limited to Determination Meetings and Agreement Meetings, refer to the guidance document entitled "Early Collaboration Meetings Under the FDA Modernization Act (FDAMA)," available at http://www.fda.gov/cdrh/ode/guidance/310.pdf, for more details on these types of pre-submission meetings.

[5] FDA intends to develop guidance on pre-submission meetings.

FDA guidance documents, as well as applicable material and testing standards related to their device type and submission.[6]

FDA notes that appeals, including requests for dispute resolution, and general policy discussions are also not within the scope of this guidance document.

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

The Least Burdensome Approach

FDA believes we should consider the least burdensome approach in all areas of medical device regulation. This guidance document reflects our careful review of the relevant scientific and legal requirements and what we believe is the least burdensome way for you to comply with those requirements. However, if you believe that an alternative approach would be less burdensome, you should contact FDA so we can consider your point of view. You may send your written comments to the contact person listed in the preface to this guidance document or to the CDRH Ombudsman. Comprehensive information on CDRH's Ombudsman, including contact information, can be found on the Internet at http://www.fda.gov/cdrh/ombudsman/.

2. Types of Interaction

FDA recommends that all appropriate forms of communication be used as tools to facilitate interactive review. Application of these communication tools for interactive review should remain flexible to balance speed and efficiency with the need to ensure appropriate FDA supervisory concurrence for significant information requests. Appropriate communication tools include email,[7] facsimile, telephone calls, meetings (i.e., telephone conferences, videoconferencing, face-to-face meetings), and letters. Regardless of which communication tool is used, FDA is ultimately responsible for ensuring a complete administrative record for each submission.

Email and Facsimile

FDA's preferred mechanisms for communication are email and facsimile because they are efficient and create a documented and permanent record of the interaction.

Telephone Calls

"One-on-one" telephone calls should be used primarily for requests for clarification that the FDA reviewer can easily document (e.g., the location of specific information within the PMA,

[6] For more information on 510(k)s and PMAs and to search for device-specific guidance documents, see CDRH's Device Advice website at http://www.fda.gov/cdrh/devadvice/. For more information on BLAs, refer to 21 CFR 601.2 and 21 CFR 601.12. For information related to standards, see ASTM International's webpage at www.astm.org and the International Standards Organization's (ISO) webpage at www.iso.org.

[7] Secure email is an option across FDA, including CDRH. It is the preferred option for CBER. A secure email account may be established by sending a request to ITCallCenter@FDA.HHS.GOV.

interpretation of a graph). Any telephone call that leads to a request for data should be followed by an email from the applicant to FDA that summarizes the commitment(s) made. FDA should respond via email to confirm the accuracy of the commitment(s) and then add the emails to the submission's official administrative record.

Meetings

Meetings are important tools for interaction. However, because meetings involve coordinating the availability of multiple FDA staff and company representatives, they typically involve additional planning and administrative efforts. Therefore, FDA and the applicant should consider whether a meeting is the most appropriate and effective communication mechanism to resolve the issue(s). Meetings are most effective when there are significant issues regarding the review that cannot be resolved by email, facsimile, or telephone calls.[8]

If FDA and the applicant both agree that a meeting is appropriate, whether during a review cycle or after a formal hold letter[9] is issued, FDA should attempt to schedule the meeting in a timely manner. In turn, the applicant should provide suggested meeting times. To make the meeting as productive as possible[10] the applicant should provide questions to be discussed at the meeting in advance.[11]

Letters

When appropriate, FDA should issue formal hold letters that will stop the review clock. Please refer to Section 8 of this guidance document for details.

3. Timing of Interaction

A cornerstone of interactive review is that interaction should occur as needed to facilitate a timely and efficient review process. With the exception of the Day 100 Meeting for PMAs, there are no fixed intervals within a review cycle or deadlines by which FDA is expected to interact with the applicant. Instead, the interactive process is driven by FDA's need, on a case-by-case basis, for additional information or clarification to complete its review and to help ensure compliance with MDUFA,[12] Office, or Center timelines.

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[8] Applicants should not request meetings for the purpose of obtaining a pre-assessment of the adequacy of data already submitted or to be submitted.

[9] For BLAs, the term "hold letter" traditionally has not been applied. Instead, CBER issues a "Complete Response Letter" to communicate deficiencies that stop the review clock for BLAs. However, for the sake of simplicity, the term "hold letter" is used in this guidance document for all submission types.

[10] CDRH intends to develop guidance on meetings with industry. For CBER submissions, refer to CBER's meeting procedures webpage at http://www.fda.gov/cber/regsopp/81011.htm.

[11] For original PMAs and panel-track supplements, FDA will grant a Day 100 Meeting upon request to discuss the review status of the application, as required by section 515(d)(3)(A)(i) of the Act, 21 U.S.C. § 360e(d)(3)(A)(i)). Please refer to the guidance document entitled, "PMA Interactive Procedures for Day-100 Meetings and Subsequent Deficiencies," available at http://www.fda.gov/cdrh/modact/day100mt.pdf, for more details.

[12] For information regarding the effect of agency and industry actions pertaining to premarket review of 510(k)s and PMAs on the FDA review clock and MDUFA goals, refer to the guidance documents entitled, "FDA and Industry Actions on Premarket Approval Applications (PMAs): Effect on FDA Review Clock and Performance Assessment," available at www.fda.gov/cdrh/mdufma/guidance/1218.html, and "FDA and Industry Actions on Premarket

When appropriate, FDA should wait until after the review of a particular topic or subject matter area (e.g., software, fatigue testing, device retrieval study) has been completed before interacting with the applicant regarding that topic to ensure that the agency communicates appropriate and comprehensive deficiencies to the applicant.

There are no pre-established timelines for applicants to respond to FDA's informal requests for additional information during the review cycle. Instead, FDA should determine the appropriate timeframe on a case-by-case basis. FDA should provide deadlines that will help ensure compliance with MDUFA, Office, or Center timelines.

4. Applicant's Role in the Interactive Review Process

What the Applicant Can Do to Help Ensure an Efficient Interactive Review Process

To help ensure that the interactive process is effective, the applicant should do the following:

- submit a complete submission consistent with applicable regulations, recommendations in the available guidance documents,[13] and communications with FDA prior to submission;
- provide complete contact information in its cover letter (i.e., name, email, phone number, fax number) accompanying each formal submission;[14]
- apply appropriate material or testing standard(s) and submit the necessary declarations or data to support the use of the standard(s);
- provide a complete response to all deficiencies communicated informally during a review cycle within the FDA-allotted timeframe;[15] and
- provide a complete response to all deficiencies cited in a formal hold letter within the specified timeframe in the letter, including reasons for responding in a different manner from that requested by FDA.[16]

Applicants should refrain from requesting mere status updates as such requests interfere with FDA's ability to comply with applicable timeframes.

Notification (510(k)) Submissions: Effect on FDA Review Clock and Performance Assessment," available at http://www.fda.gov/cdrh/mdufma/guidance/1219.html.

[13] For more information on 510(k)s and PMAs and to search for device-specific guidance documents, see CDRH's Device Advice website at http://www.fda.gov/cdrh/devadvice/. For more information on BLAs, refer to 21 CFR 601.2 and 21 CFR 601.12.

[14] FDA also recommends providing alternative contact information in case the lead contact is not available. In addition, foreign applicants should have a U.S. representative available to participate in the interactive review process and to provide a means to contact the foreign company as quickly as possible.

[15] A complete response is one in which the applicant provides the requested information or an alternative means of addressing each cited deficiency.

[16] Partial responses are not conducive to a timely review and will not restart the review clock.

Examples of When the Applicant Should Contact the FDA Lead Reviewer

Examples of when the applicant should contact the lead reviewer of the submission[17] during the course of review include the following:

- to obtain clarification regarding deficiencies cited by the lead reviewer;

  It is important to note that, although FDA should provide clarification regarding deficiencies, the applicant should not contact FDA to request that FDA review proposed responses addressing the cited deficiencies for adequacy. Instead, the applicant should submit its official response to FDA for review when the response is complete.

- to reconcile any disagreement with a deficiency cited by a consulting reviewer;

- to inquire whether a new timeframe may be given to address a deficiency during a review cycle because the initial timeframe cannot be met;

- to discuss procedural questions related to the submission;

- to correct errors in the data submitted;

- to clarify information in the submission that the applicant subsequently notices is unclear;

- to request or schedule a meeting; or

- to alert FDA that it intends to submit new, unsolicited information or data (depending on its extent, the information/data may require a new 510(k) or be logged in as an unsolicited major amendment for a PMA, PMA supplement, BLA, or BLA Supplement).

In addition to contacting the lead reviewer in the instances listed above, the applicant should also contact the consulting reviewer directly to obtain clarification regarding deficiencies cited by the consulting reviewer.

5. FDA's Role in the Interactive Review Process for 510(k)s

When appropriate, FDA should interact with the 510(k) applicant[18] by phone, email, and/or facsimile to resolve outstanding issues until either a final decision can be made or FDA is ready to place the 510(k) on hold because it has completed its review and can only continue the review when the applicant provides the requested information. See Section 8 below.

When FDA requests additional information through the interactive review process, the agency should determine an acceptable timeframe for submission of the response. The established timeframe should be based on the impending review deadline, the estimated time that the applicant should need to respond, and the estimated time that FDA should need to review the response.

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[17] The lead reviewer is a reviewer assigned to lead a group of consulting reviewers (e.g., clinician, statistician, scientist(s)) through the review of a premarket submission.

[18] An applicant for a 510(k) is the same as the 510(k) holder or submitter for the purposes of this guidance document.

FDA should accept informal responses to the requested information and include that information as part of the official review record for the submission. FDA should not request the response to be submitted by the applicant as part of an official submission to the CDRH Document Mail Center (DMC)[19] unless warranted by the circumstances. We expect that there will be few requests for official submissions to DMC within a review cycle. Minimizing the number of submissions to DMC reduces the administrative burden of processing official submissions for every interaction between FDA and the applicant.

If the applicant does not provide a response to a deficiency within the timeframe allotted by FDA, then the issue identified in the communication from FDA should serve as an alert to the applicant of an issue that will be included in a 510(k) formal hold letter once FDA completes its review, which stops the review clock. The applicant should then wait until it has received the formal hold letter before submitting a complete response to DMC that addresses all of the deficiencies identified by FDA.[20]

Examples of information that FDA should request informally through the interactive review process prior to putting a 510(k) on hold includes the following:

- revisions to administrative items (e.g., 510(k) Summary/Statement, Indications for Use statement);
- a more detailed device description;
- omitted engineering drawings;
- clarification of preclinical test methodology, results (including summary data tables, graphs, and figures), and conclusions;
- clarification of sterilization validation procedures; and/or
- labeling revisions.

[19] The Document Mail Center serves as the Center's gateway for receiving official submissions, which must be sent via mail (e.g., (1) a complete response to a formal letter placing a submission on hold, which allows a release of the submission from on-hold status or (2) additional information requested during the interactive review for which an informal response is not sufficient). See Section 8. The CBER equivalent to the CDRH DMC is the CBER Document Control Center (DCC). For the purposes of this guidance, references to the DMC cover both the CDRH DMC and CBER DCC.

[20] If the applicant provides unsolicited information that significantly changes the content of the 510(k) (e.g., change in indication, modified design, modified materials), then FDA may place the 510(k) on hold to request a separate 510(k) for the significantly modified device. Refer to the guidance document entitled, "User Fees and Refunds for Premarket Notification Submissions (510(k)s)," available at http://www.fda.gov/cdrh/mdufma/guidance/1511.pdf, for more details.

6. FDA's Role in the Interactive Review Process for PMAs and BLAs

Minor Issues

When appropriate, FDA should interact with the PMA/BLA applicant by phone, email, and/or facsimile to resolve minor issues/deficiencies (i.e., those that do not warrant substantive review or analysis).

When a request involves minor deficiencies, FDA should determine an acceptable timeframe for the applicant to provide a response. The established timeframe should be based on the impending review deadline, the estimated time that the applicant should need to respond, and the estimated time that the FDA should need to review the response.

FDA should accept informal responses to the requested information and include that information as part of the official review record for the submission. FDA should not request the response to be submitted by the applicant as part of an official submission to DMC unless warranted by the circumstances. We expect that there will be few requests for official submissions to DMC within a review cycle. Minimizing the number of submissions to DMC reduces the administrative burden of processing official submissions for every interaction between FDA and the applicant.

If the applicant does not provide a response addressing the minor deficiencies cited by FDA within the timeframe allotted, then the communication from FDA should serve as an alert to the applicant of an issue that will be included in a forthcoming formal hold letter once FDA completes its review, which stops the review clock. The applicant should then wait until it has received the formal hold letter before submitting a complete response to DMC that addresses all of the deficiencies identified by FDA.

Examples of minor issues that FDA should resolve informally through the interactive review process include the following:

- revisions to certifications (e.g., environmental impact assessment, financial disclosure statements);
- a more detailed device description;
- omitted engineering drawings;
- clarification of preclinical test methodology, results (including summary data tables, graphs, and figures), or conclusions;
- omitted manufacturing documents/procedures;
- clarification of clinical data;
- clarification of sterilization validation procedures;
- labeling revisions;

- summary of pertinent literature; and/or
- postapproval study plans.

Depending on the nature and significance of an outstanding issue, some of the examples listed above may be considered major issues rather than minor issues.

Major Issues

Although the primary focus of interactive review between FDA and the applicant is on resolving minor issues informally, when appropriate FDA should also informally communicate major issues to the applicant.

Prior to communicating any major issue to the applicant, the issue should first be reviewed and approved by both the lead reviewer and the lead reviewer's management in order to ensure its consistency with current policy or practice. FDA should not informally communicate major issues regarding a specific topic if other information in the submission may change the outstanding issue or negate it (e.g., an animal study may address an outstanding bench test issue). Instead, FDA should wait to communicate a major issue until it has a complete overview of the information submitted. Therefore, the applicant should note that major issues not previously communicated to the applicant may be included in a formal hold letter from FDA.[21]

Any communication of a major issue should serve only to alert the applicant to an issue that will be included in a forthcoming formal hold letter.[22] Some major issues may be informally communicated in detail sufficient to permit the applicant to begin addressing the concerns before the issuance of a formal hold letter. However, for major issues, FDA does not expect any response to be submitted within the current review cycle; thus, FDA should not provide a timeframe for responding. Instead, the applicant should wait until it has received a formal hold letter and then submit to DMC a complete response that addresses all deficiencies identified by FDA. We believe that this early communication will minimize the amount of time necessary for the applicant to respond to a formal hold letter.

If the applicant submits a response to a major issue prior to FDA issuing a formal hold letter then FDA should process the information as an unsolicited major amendment. This extends the review time for the FDA reviewer, as permitted by 21 CFR 814.37(c)(1).[23] FDA discourages this approach as it would delay completion of the review for that cycle and the issuance of a formal letter detailing all outstanding issues. In turn, this extends the overall review time for a submission.

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[21] FDA cannot determine the appropriate letter (e.g., major deficiency, not approvable, approvable pending deficiencies) to send until it completes the review. See Section 8 below. Discussion regarding FDA's overall decision for a review cycle is not a goal of interactive review.

[22] If an applicant believes that it has already addressed a major issue with the data submitted, then the applicant should contact the lead reviewer to discuss the issue. If appropriate, the lead reviewer may request the applicant to provide its rationale explaining why the existing data addresses the issue.

[23] See the guidance document entitled, "FDA and Industry Actions on Premarket Approval Applications (PMAs): Effect on FDA Review Clock and Performance Assessment," available at www.fda.gov/cdrh/mdufma/guidance/1218.html, for details.

Examples of major issues include the need for:

- additional preclinical testing;
- supplemental bench, animal, or clinical information to address a specific safety issue;
- a new statistical analysis of the submitted clinical data set; and/or
- additional manufacturing procedures.

7. FDA Review Team Considerations

As appropriate, the lead reviewer should establish a review team of consulting reviewers with diverse expertise to review complex submissions. Consulting reviewers, like the lead reviewer, should expect to participate in the interactive review of submissions; however, the lead reviewer should determine whether or not a consulting reviewer should directly communicate with the applicant or communicate to the applicant through the lead reviewer.

In cases where a consulting reviewer communicates directly with the applicant on a particular issue, a documented record of the exchange should be made available to the lead reviewer (e.g., "cc" on an email).

As stated above, major deficiencies should be communicated from/to the lead reviewer and the lead reviewer's management for their review and approval prior to communicating with the applicant.

8. Placement of Submission on Hold

A submission should be placed on hold when FDA has completed the review of the entire submission for that review cycle in accordance with MDUFA, Office, or Center timelines, and FDA is ready to relay outstanding issues to the applicant.

510(k)

To place a 510(k) on hold, the review division should either:

- send the applicant an Additional Information (AI) letter that includes the final set of deficiencies; or
- communicate the final set of deficiencies to the applicant via phone, email, or facsimile. If this option is used, then DMC should issue a computer-generated boilerplate hold letter to the applicant. The computer-generated hold letter should not include the outstanding issues in the body of the letter as these issues already should have been communicated to the applicant via phone, email, or facsimile.

A 510(k) submission should not be considered officially on hold until it is processed through the DMC.[24]

[24] All hold and final decision letters should be faxed (if the applicant has provided a fax number in its cover letter) and mailed to the applicant.

FDA should remove a 510(k) from an on-hold status and return it to an under-review status (at which time the review clock resumes) only when DMC receives an official submission from the applicant that includes complete responses to all outstanding issues.

PMA or BLA

To place a PMA or BLA on hold, the review division should send the applicant the appropriate hold letter (e.g., major deficiency letter, not approvable letter, approvable pending deficiencies letter, or, for BLAs, Complete Response letter).[25] The letter should include:

- minor deficiencies that remain unresolved because the applicant failed to respond or provided an inadequate response to an FDA request during the interactive process;
- new deficiencies that FDA did not previously communicate to the applicant because FDA only became aware of the deficiencies in the latter part of the review cycle (e.g., if a reanalysis of the data or testing was necessary to define the outstanding issue);
- deficiencies that cannot be handled through the interactive review process because of the extensive time required for the applicant to collect, analyze, and provide the data; and/or
- major deficiencies that FDA did not previously communicate to the applicant because they are controversial in nature and thus required extensive deliberation by FDA management to ensure consistency with FDA regulations, review policies, and practices.

FDA should remove a PMA or a BLA from an on-hold status and return it to an under-review status (at which time the review clock resumes) only when DMC receives an official submission from the applicant that includes complete responses to all outstanding issues cited in the hold letter.[26]

[25] All hold and final decision letters should be faxed (if the applicant has provided a fax number in its cover letter) and mailed to the applicant.

[26] For original PMAs and panel track supplements, the CDRH Office of Compliance issues its own manufacturing deficiency letters. These particular letters do not impact the MDUFA timeframes.