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# Developing and Responding to Deficiencies in Accordance with the Least Burdensome Provisions

## 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 Regulatory Programs 1 at 301-796-5640 or by email at opeqsubmissionsupport@fda.hhs.gov.

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**U.S. Department of Health and Human Services**
**Food and Drug Administration**
**Center for Devices and Radiological Health**
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# Preface

## Public Comment

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# Developing and Responding to Deficiencies in Accordance with the Least Burdensome Provisions

# 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

This guidance document is intended to help Food and Drug Administration (FDA) staff develop a request for additional information needed to make a decision on a medical device marketing application in accordance with the Least Burdensome Provisions of the Federal Food, Drug, and Cosmetic Act (FD&C Act). Such an FDA request for additional information is known as a "deficiency." In addition, this guidance describes suggested formats for FDA staff to communicate deficiencies, and for industry to use for responses to such requests, in order to make efficient use of industry and FDA's time. This guidance includes examples of well-constructed deficiencies and industry responses to facilitate an efficient review process. This guidance also details supervisory review, major/minor deficiencies, additional considerations, and prioritization of deficiencies in FDA deficiency letters.

For the current edition of the FDA-recognized consensus standard(s) referenced in this document, see the FDA-Recognized Consensus Standards Database.[1]

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

[1] Available at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm.

use of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

Throughout this guidance document, the terms "we," "us," and "our" refer to FDA staff from the Center for Devices and Radiological Health (CDRH) or the Center for Biologics Evaluation and Research (CBER) involved in the review and decision-making aspects of a marketing application. "You," "your," or "applicant" refer to the submitter of a premarket application.

# II. Background

FDA review staff often identify the need for additional information in order to make a premarket approval (PMA) determination of reasonable assurance of safety and effectiveness (RASE), a humanitarian device exemption (HDE) determination of safety and probable benefit, a 510(k) determination of substantial equivalence (SE), or a classification determination for a De Novo request. Throughout this guidance document, PMA, 510(k), HDE, and De Novo premarket submissions will be collectively called "marketing applications." In addition, throughout this guidance document, the FDA decisions made on these applications will be collectively called "marketing authorization decisions" (e.g., PMA reasonable assurance of safety and effectiveness determination, 510(k)substantial equivalence determination, HDE safety and probable benefit determination, and De Novo classification determination). FDA's requests for additional information needed to complete the review process are colloquially known as "deficiencies."

FDA may convey deficiencies via interactive review or through a deficiency letter. In general, FDA uses interactive review to attempt to resolve minor deficiencies and additional considerations with the applicant by phone or email without putting the submission officially on hold. Deficiency letters are delivered via email and generally include at least one major issue and place the marketing application on hold pending FDA's receipt of the requested additional information. FDA refers to PMA and HDE deficiency letters as "major deficiency letters" and 510(k) and De Novo deficiency letters as "additional information letters" or "requests for additional information." For more information about interactive review and when medical device submissions are placed on hold, see the FDA guidance documents "Types of Communication During the Review of Medical Device Submissions,"[2] "FDA and Industry Actions on Premarket Notification (510(k)) Submissions: Effect on FDA Review Clock and Goals,"[3] "FDA and Industry Actions on Premarket Approval Applications

[2] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/types-communication-during-review-medical-device-submissions.
[3] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-and-industry-actions-premarket-notification-510k-submissions-effect-fda-review-clock-and-goals.

(PMAs): Effect on FDA Review Clock and Goals,"[4] and "FDA and Industry Actions on De Novo Requests: Effect on FDA Review Clock and Goals."[5]

Minor deficiencies may still be included in deficiency letters when related to the resolution of substantive issues (e.g., modification of the proposed Indications for Use may lead to revisions in labeling and administrative items), or if they were still unresolved following interactive review attempts. Additional considerations may also be included in deficiency letters if left unresolved following interactive review attempts, but would not require an applicant response.

The Least Burdensome Provisions of the Food and Drug Administration Modernization Act (FDAMA) were added to the FD&C Act in 1997. The Least Burdensome Provisions were amended by the Food and Drug Administration Safety and Innovation Act (FDASIA) and the 21st Century Cures Act and state that:

- "Whenever the Secretary requests information to demonstrate that devices with differing technological characteristics are substantially equivalent, the Secretary shall only request information that is necessary to making substantial equivalence determinations. In making such request, the Secretary shall consider the least burdensome means of demonstrating substantial equivalence and request information accordingly."[6]

- "Any clinical data, including one or more well-controlled investigations, specified in writing by the Secretary for demonstrating a reasonable assurance of device effectiveness shall be specified as result of a determination by the Secretary that such data are necessary to establish device effectiveness. The Secretary shall consider, in consultation with the applicant, the least burdensome appropriate means of evaluating device effectiveness that would have a reasonable likelihood of resulting in approval."[7]

- In requesting additional information with respect to a PMA application, "the Secretary shall consider the least burdensome appropriate means necessary to demonstrate a reasonable assurance of device safety and effectiveness."[8]

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[4] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-and-industry-actions-premarket-approval-applications-pmas-effect-fda-review-clock-and-goals.
[5] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-and-industry-actions-de-novo-classification-requests-effect-fda-review-clock-and-goals.
[6] See FD&C Act, Section 513(i)(1)(D)(i).
[7] See FD&C Act, Section 513(a)(3)(D)(ii).
[8] See FD&C Act, Section 515(c)(5)(A).

- "The Secretary shall consider the role of postmarket information in determining the least burdensome means of demonstrating a reasonable assurance of device safety and effectiveness."[9]

- The Secretary shall only request the "minimum required information" necessary to support a determination of substantial equivalence or a reasonable assurance of safety and effectiveness of the device.[10]

- The Least Burdensome Provisions do not change the standards for premarket approval or substantial equivalence.[11]

Information about specific approaches to the Least Burdensome Provisions are detailed in the FDA guidance document "The Least Burdensome Provisions: Concept and Principles."[12] Additionally, the Agency's approach to least burdensome principles in 510(k) submissions is discussed in the FDA guidance document "The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]."[13]

Under section 513(a)(2) of the FD&C Act, FDA determines the "safety and effectiveness of a device" by "weighing any probable benefit to health from the use of the device against any probable risk of injury or illness from such use," among other relevant factors.[14] The least burdensome principles are also consistent with FDA's approach to evaluating the benefit-risk profile in marketing authorization decisions for medical devices. Further, marketing authorization decisions may involve some degree of uncertainty about the benefits and risks of a medical device. In some circumstances, greater uncertainty may be appropriate, such as when the probable benefits are high or the probable risks of the device are low. As part of considering and applying the tenets of least burdensome principles, the factors of benefit, risk and uncertainty are also considered as appropriate. For additional information and a fuller explanation of how FDA may consider these factors in marketing authorization decisions, please see FDA's guidance documents entitled "Benefit-Risk Factors to Consider When Determining Substantial Equivalence in Premarket Notifications (510(k)) with Different Technological Characteristics,"[15] "Factors to Consider When Making Benefit-Risk

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[9] See FD&C Act, Section 515(c)(5)(C).
[10] See FD&C Act, Sections 513(i)(1)(D)(ii), 513(a)(3)(D)(iii), and 515(c)(5)(B).
[11] See FD&C Act, Sections 513(i)(1)(D)(iii), 513(a)(3)(D)(iv), and 515(c)(5)(D).
[12] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/least-burdensome-provisions-concept-and-principles.
[13] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/510k-program-evaluating-substantial-equivalence-premarket-notifications-510k.
[14] The criteria for establishing safety and effectiveness of a device are set forth in 21 CFR 860.7. Subsection (b) notes, "[i]n determining the safety and effectiveness of a device…the Commissioner and the classification panels will consider the following, among other relevant factors… (3) The probable benefit to health from the use of the device weighed against any probable injury or illness from such use." (21 CFR 860.7(b)). For additional information on FDA's safety and effectiveness review, see 21 CFR 860.7(d) and (e).
[15] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/benefit-risk-factors-consider-when-determining-substantial-equivalence-premarket-notifications-510k.

Determinations in Medical Device Premarket Approval and De Novo Classifications,"[16] and "Consideration of Uncertainty in Making Benefit-Risk Determinations in Medical Device Premarket Approvals, De Novo Classifications, and Humanitarian Device Exemptions."[17]

In the Medical Device User Fee Amendments of 2022 (MDUFA V) Commitment Letter from the Secretary of Health and Human Services to Congress,[18] FDA committed to update this guidance document to "clarify what constitutes a statement of basis for the deficiency and continue alignment with the following:

> "Deficiency letters should include a statement of the basis for the deficiencies (e.g., a specific reference to applicable section(s) of a rule, final guidance, recognized standard unless the entire or most of document is applicable). In the instance when the deficiency cannot be traced in the manner above and relates to a scientific or regulatory issue pertinent to the determination, FDA will cite the specific scientific issue and the information to support its position.
>
> "Deficiency letters will undergo supervisory review prior to issuance to ensure the deficiencies cited are relevant to a marketing authorization decision (e.g., 510(k) clearance, PMA approval, and [D]e [N]ovo classification)."

# III. Scope

This guidance is intended to help FDA review staff and supervisors develop deficiencies for inclusion in deficiency letters for medical device marketing applications. While FDA review staff may use a similar deficiency format for interactive review, investigational device exemption applications (IDEs), 513(g) requests for information, and Q-Submissions, this guidance document only applies to deficiency letters sent during the review of marketing applications. This guidance will also aid industry in preparing responses to deficiency letters. Examples of different types of FDA deficiencies along with rationales to support such requests for information, as well as examples of different approaches to respond to FDA deficiencies, are included in Appendix A.

# IV. Deficiency letters in marketing applications

## A. Guiding principles

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[16] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/factors-consider-when-making-benefit-risk-determinations-medical-device-premarket-approval-and-de.

[17] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/consideration-uncertainty-making-benefit-risk-determinations-medical-device-premarket-approvals-de.

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

In using this guidance document, FDA review staff should follow these guiding principles regarding the development of deficiency letters:

1. Information unrelated to the marketing authorization decision should not be part of the decision-making process.

2. Alternative approaches to resolving regulatory issues should be considered to optimize the necessary time, effort, and resources involved in developing a response.

3. Deficiencies should request the minimum (i.e., least burdensome) amount of information necessary to adequately address the identified issue in the most efficient manner at the right time. The balance between premarket and postmarket should be considered to determine when information should be provided to address the identified issue.[19]

4. The totality of the information necessary for evaluating the benefit-risk profile of the device[20] as well as uncertainty in making benefit-risk determinations for PMAs and De Novos should be considered.[21]

5. Major deficiencies are those based on least burdensome principles that, if not resolved, will preclude a favorable marketing authorization decision. Major deficiencies should only be included if their resolution is necessary in order to reach a final decision.

6. If the Agency is including minor deficiencies identified during the review in the deficiency letter, the Agency should identify these requests separately from major issues, and whenever possible, attempt to resolve minor questions/issues interactively. Minor deficiencies are FDA requests that can be resolved in a straightforward manner, but that need to be addressed to meet regulatory requirements or to prevent potential misbranding or adulteration. In

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[19] See also The Least Burdensome Provisions: Concept and Principles, available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/least-burdensome-provisions-concept-and-principles.

[20] See Benefit-Risk Factors to Consider When Determining Substantial Equivalence in Premarket Notifications (510(k)) with Different Technologial Characteristics, available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/benefit-risk-factors-consider-when-determining-substantial-equivalence-premarket-notifications-510k and Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications, available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/factors-consider-when-making-benefit-risk-determinations-medical-device-premarket-approval-and-de.

[21] See Consideration of Uncertainty in Making Benefit-Risk Determinations in Medical Device Premarket Approvals, De Novo Classifications, and Humanitarian Device Exemptions, available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/consideration-uncertainty-making-benefit-risk-determinations-medical-device-premarket-approvals-de.

general, the Agency should not issue a formal deficiency letter if only minor deficiencies remain, but instead should attempt to resolve them interactively.

7. FDA may also include additional considerations that are suggestions, recommendations, or requests that are not expected to preclude a favorable marketing authorization decision. Because additional considerations are not expected to preclude a favorable decision, they do not require an applicant response.

## B. Suggested content and format for deficiencies

An effective deficiency should concisely include the following four elements:

1. **What was submitted:** Acknowledgment of the information submitted by the applicant, including references to sections, page numbers, or tables where appropriate.

2. **Identification of a specific issue or concern**[22] with information that was submitted, is missing, or is inadequate.

3. **Statement of basis for the deficiency**[23] that includes the effect or impact of the specific issue or concern on the marketing authorization decision,[24] and, when available, applicable, and relevant, a specific reference.[25]

4. **Explicit request for the additional information needed** to address the issue and potential alternate ways of satisfying the issue, if applicable.

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[22] A specific issue or concern can be scientific, clinical, and/or regulatory in nature.

[23] The commitment letter states that FDA will clarify what constitutes a statement of the basis for the deficiency and continue alignment with the following principle: "Deficiency letters should include a statement of the basis for the deficiencies (e.g., a specific reference to applicable section of a rule, final guidance, recognized standard unless the entire or most of document is applicable). In the instance when the deficiency cannot be traced in the manner above and relates to a scientific or regulatory issue pertinent to the determination, FDA will cite the specific scientific issue and the information to support its position." FDA's definition of the "statement of basis for the deficiency" in this guidance clarifies that an effective deficiency should include the "specific scientific issue and the information to support its position" (i.e., "effect or impact of the specific issue on the marketing authorization decision") regardless of whether or not a specific reference is available, applicable, and relevant. This is also consistent with FDA's long-standing policy, as described in previous versions of this guidance.

[24] The effect or impact of the specific issue or concern on the marketing authorization decision encompasses the elements of the statutory standard for each submission type, including but not limited to, the impact on device safety or effectiveness, the device's benefit-risk profile, and/or the uncertainty in making the benefit-risk determination of a device.

[25] A specific reference is an applicable section of a final rule or statute, or a recommendation provided through an applicable section of a final guidance or FDA-recognized consensus standard (unless the entire or most of the reference is applicable).

FDA review staff may include more than one statement for each element or alter the order of the elements listed above to represent a logical thought flow or because the concepts may be intertwined. Additionally, FDA review staff may include an introductory paragraph to the deficiency letter, or a preface for multiple deficiencies on a single topic, to improve clarity and reduce redundant language. Examples of deficiencies with different structures are included in Appendix A for reference.

### C. Review of deficiency letters

As stated in the MDUFA V Commitment Letter, deficiency letters will undergo supervisory review prior to issuance to ensure the deficiencies cited are relevant to the marketing authorization decision. Supervisory review should also ensure deficiencies include the four elements described above in Section IV.B of this guidance. This supervisory review should ensure that "specific references" are included in deficiencies (when such references are available, applicable, and relevant), and if any deficiencies do not include "specific references", verify such exclusions are appropriate. FDA staff and managers should ensure that deficiencies are prioritized according to the Agency's view of their significance. The most significant deficiencies should be listed first in deficiency letters. During their review, FDA managers should also consider the totality of all deficiencies to determine whether each individual request is still appropriate.

## V. Suggested format for industry responses to FDA deficiencies

Applicants should provide complete responses to all deficiencies within the timeframe indicated in FDA's deficiency letter. For more information about deficiency letter responses and their impact on the FDA review clock, see "FDA and Industry Actions on Premarket Notification (510(k)) Submissions: Effect on FDA Review Clock and Goals,"[26] "FDA and Industry Actions on Premarket Approval Applications (PMAs): Effect on FDA Review Clock and Goals,"[27] and "FDA and Industry Actions on De Novo Requests: Effect on FDA Review Clock and Goals." [28]

FDA recommends the following format for applicants when responding to deficiencies:

1. Restate the identified Agency issue; and

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[26] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-and-industry-actions-premarket-notification-510k-submissions-effect-fda-review-clock-and-goals.
[27] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-and-industry-actions-premarket-approval-applications-pmas-effect-fda-review-clock-and-goals.
[28] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-and-industry-actions-de-novo-classification-requests-effect-fda-review-clock-and-goals.

2. Provide one of the following:

   a. the information or data requested;

   b. an explanation why the issue does not affect or impact the marketing authorization decision; or

   c. alternative information and an explanation describing why the information adequately addresses the issue.

FDA recommends that applicants provide the deficiency number and an identical restatement of the Agency's question when responding to a particular deficiency. If you are responding to a follow-up question from a previous deficiency, FDA recommends that you include both the original deficiency and follow-up question in advance of providing your response to such deficiency. If your response is extensive, we recommend that you organize the information with a table of contents, list of figures, and/or list of tables, as necessary to facilitate ease of review. In your response to deficiencies, you should include a description or justification of how the information adequately addresses the Agency's concern(s). When providing a declaration of conformity to FDA-recognized consensus standards in lieu of data, you should identify the standard, its revision date, applicable sections, and any deviations from the standard. For more information about consensus standards in regulatory submissions, please refer to the FDA guidance titled "Appropriate Use of Voluntary Consensus Standards in Premarket Submissions for Medical Devices"[29] and "Standards Development and the Use of Standards in Regulatory Submissions Reviewed in the Center for Biologics Evaluation and Research."[30]

As stated in 2b of FDA's recommendations on how to respond to a deficiency above, if you believe that the Agency's request is not relevant to the marketing authorization decision, you should provide a justification in your response to FDA's deficiency letter. For 510(k) submissions, if a legally marketed predicate is available to support your response, you should also reference the relevant 510(k) number.

As stated in 2c above, in formulating your response, you may consider suggesting alternate approaches to optimize the time, effort, and cost of resolving the issue within the applicable statutory and regulatory criteria for the marketing authorization decision. This alternate approach could include different types of bench testing, proposing non-clinical testing in lieu of clinical testing, or conformance to FDA-recognized consensus standards. If an alternative approach is taken, you should discuss how the included information satisfies applicable statutory and regulatory criteria for the marketing authorization decision.

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[29] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/appropriate-use-voluntary-consensus-standards-premarket-submissions-medical-devices.

[30] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/standards-development-and-use-standards-regulatory-submissions-reviewed-center-biologics-evaluation.

# Appendix A: Deficiency and applicant response examples

The following example deficiencies and applicant responses are only intended to illustrate the principles and recommendations discussed in this guidance document. For illustrative purposes, we have enumerated each portion of the deficiencies below in brackets to demonstrate how each example includes the four elements described in Section IV. B above. FDA does not intend to enumerate each element of the deficiency format in deficiency letters. Additionally, we have indicated the type(s) of marketing application(s) for which the example deficiency and applicant response may be relevant.

As noted in Section V, FDA recommends that applicants provide the deficiency number and an identical restatement of the Agency's question when responding to a particular deficiency. However, in the examples below, we have omitted the restatement of the Agency's question for purposes of simplicity. Some examples also include justifications in lieu of the requested information. Although justifications are provided to demonstrate potential alternative approaches, it should not be inferred that such responses would necessarily be considered to be adequate to support a particular marketing authorization.

1. **Statement of basis for the deficiency with specific reference to final rule or statute**

   **FDA deficiency:**
   [1] In your device description on page 5, you stated that the oscillation frequency of the device is 8 – 12 Hz, and you provided results from performance testing of the handpiece in a test report (in Appendix A). [2] However, the test results you provided did not include an evaluation of puncture rate [3] as required by the special control specified in 21 CFR 878.4430(b)(2)(i). [4] Please provide bench performance data to demonstrate that the puncture rate is within the specified operating frequency of 8 – 12 Hz across the device's operating parameters. We recommend that your puncture rate testing be conducted using a test set-up that is representative of a clinically relevant worst-case scenario. Please also include a rationale in your test report for the test parameters you have chosen, including the test set-up, clinically relevant substrate, and acceptance criteria. *[Relevant to 510(k)s only]*

   **Applicant response:**
   We did not include the requested testing because the proposed device only includes modifications from our own predicate that did not affect the puncture rate of the device. Since we have not changed the puncture rate nor would any of the device changes since the last 510(k) clearance impact the device's puncture rate performance, the test results from our predicate device to demonstrate the puncture rate is within the specified operating frequency (of 8 – 12 Hz) are still applicable (Reference Kxxxxxx). *[Relevant to 510(k)s only]*

2. **Statement of basis for the deficiency with specific reference to final rule or statute and final guidance document**

**FDA deficiency:**
[1] Based on information in your submission (Section 1), your device is supplied sterile and requires the user to reprocess after the initial use and prior to subsequent patient use. [2] However, your provided labeling (in Section 10) did not include reprocessing instructions. Instructions on how to adequately reprocess a device of this type are critical to ensuring that it is appropriately prepared for its subsequent use [3] and to reduce the risk of infection in patients from an improperly reprocessed device. Further, as stated in Section II of FDA's guidance document "Reprocessing Medical Devices in Health Care Settings: Validation Methods and Labeling" (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/reprocessing-medical-devices-health-care-settings-validation-methods-and-labeling), for reprocessed devices, FDA interprets adequate reprocessing instructions to be important to comply with labeling requirements for prescription use devices per 21 CFR 801.109(c) and section 502(f) of the Federal Food, Drug, and Cosmetic Act. [4] Therefore, please add validated reprocessing instructions to your device labeling to sufficiently mitigate the risks associated with multiple uses of your device for the intended patient population. Additional recommendations regarding the content of reprocessing instructions may be found [3] in Section V and VI of FDA's guidance document "Reprocessing Medical Devices in Health Care Settings: Validation Methods and Labeling. *[Relevant to all marketing applications]*

**Applicant response:**
We have added validated reprocessing instructions to our device labeling, consistent with the recommendations outlined in the FDA guidance "Reprocessing Medical Devices in Health Care Settings: Validation Methods and Labeling." The updated labeling is in Section 5 of this response. *[Relevant to all marketing applications]*

3. **Statement of basis for the deficiency with specific reference to FDA-recognized consensus standard**

**FDA deficiency:**
[1] You provided irritation test results in Appendix C that you stated are in accordance with FDA-recognized consensus standard ISO 10993-23 *Biological evaluation of medical devices — Part 23: Tests for irritation*. [2] However, the results from your polar extract failed to meet the acceptance criteria of this test [3] as described in ISO 10993-23:2021, Clause 7.3.7 and [2] you have not provided a corresponding justification to support why this failure does not raise safety concerns regarding your device's biocompatibility profile. These results raise concerns about the irritation risk from your device, [3] because exposure to the device (if it includes even a small amount of an irritant) can result in a localized non-specific inflammatory response, which can lead to redness, swelling, itching, dryness, cracking of the skin, blistering or pain. [4] Therefore, please provide a justification for acceptance of the failed irritation testing including an explanation of how you determined that your device demonstrates

acceptable biocompatibility. Please note that depending on the justification provided, information from a root cause analysis and/or additional testing (e.g., comparison to a legally US-marketed device with similar materials and the same intended use) may be necessary to demonstrate the safety of your product. *[Relevant to all marketing applications]*

**Applicant response:**
As the results of testing with polar extract of the device were inconsistent between the animals, we repeated the test with the polar extract of the device using three additional rabbits according to the recommendation provided in clause 7.3.7 in ISO 10993-23. The repeat test results met the test acceptance criteria of this standard, demonstrating mitigated irritation risk and acceptable biocompatibility. Please see Attachment II for the results. *[Relevant to all marketing applications]*

4. **Statement of basis for the deficiency with specific reference to final guidance document**

**FDA deficiency:**
[1] You stated on page 5 that, based on the coating integrity testing and results provided in Section 18, your device is equivalent to the predicate device and therefore additional particulate testing is not needed. [2] Although your coating integrity testing has not shown any flaking or coating defects, the dimensional and coating changes that you made to your device (as compared to the predicate) could still result in increased particulate generation. This is a concern [3] as particulate generation during clinical use may result in serious adverse events including pulmonary embolism, pulmonary infarction, myocardial embolism, myocardial infarction, embolic stroke, tissue necrosis and death. [4] Therefore, please provide the results of particulate testing conducted on your device at baseline and at the end of your labeled shelf life (T = 12 months) in a simulated use model that is reflective of a sufficiently challenging case in order to capture an estimation of particulates that could be released during clinical use. [3] Consistent with the recommendations in Section IV.G.11 of FDA Guidance "Coronary, Peripheral, and Neurovascular Guidewires – Performance Tests and Recommended Labeling" (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/coronary-peripheral-and-neurovascular-guidewires-performance-tests-and-recommended-labeling), [4] we also recommend that as part of this testing, the number of particulates generated at each evaluation be quantified and characterized by size and count using a validated method (e.g., light obscuration, light refraction) under continuous flow conditions to simulate blood flow. Specifically, we recommend that the total number of particulates be reported in the following size ranges: ≥ 10µm, ≥ 25µm, and at the largest size for which validation yields ≥ 75% recovery. We also recommend that appropriate precautions be implemented to ensure that particulates are suspended during particulate counting and sizing to minimize the risk of undercounting. *[Relevant to 510(k)s only]*

**Applicant response:**
We have included study results for particulate generation testing (in Section V) to address the Agency's concern regarding the modifications to the coating and the dimensional

changes to the subject device. These results are presented with a direct comparison, in the same simulated use model, to the predicate device to better demonstrate substantial equivalence. *[Relevant to 510(k)s only]*

5. **Statement of basis for the deficiency with specific reference to final guidance document and FDA-recognized consensus standard**

**FDA deficiency:**
[1] You indicated that your home use device includes smart lithium-ion battery packs (batteries hereafter) that the user needs to detach from the host device to recharge (page 13). [2] However, you have not provided electrostatic discharge (ESD) immunity testing for the batteries separately from the evaluations for the complete device. [3] As described in Section IV.E of the FDA Guidance "Electromagnetic Compatibility (EMC) of Medical Devices" (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/electromagnetic-compatibility-emc-medical-devices), [2] this is a concern as ESD can damage the battery's electronic components, [3] which can lead directly to patient harm (e.g., burn from overcharge). [2] Damaged battery electronic components can also lead to premature battery depletion, [3] which can interrupt patient treatment and result in adverse clinical impacts. [4] Therefore, please provide an ESD test protocol and test report for the batteries independently after removal from the device. We recommend using test methods [3] consistent with the current FDA-recognized version of IEC 60601-1-2 *Medical electrical equipment – Part 1-2: General requirements for basic safety and essential performance – Collateral Standard: Electromagnetic disturbances – Requirements and tests* (Clause 8), as well as the test criteria specified in Table 4 or Table 8 from the same standard. *[Relevant to all marketing applications]*

**Applicant response:**
We have included an ESD test report for the device's smart lithium-ion battery pack, removed from the device and tested separately (see Section 2). The ESD protocol used is the same as the one we used for another one of our devices in a separate, recently authorized marketing submission (see *[specific submission number]*). The ESD protocol from that previously authorized device is applicable to this device because they both have a similar intended use and both use a similar smart, removable, rechargeable battery pack. The ESD protocol is also consistent with the test methods and criteria specified in the current FDA-recognized version of IEC 60601-1-2. *[Relevant to all marketing applications]*

6. **Statement of basis for the deficiency without specific reference to final rule, statute, FDA-recognized consensus standard, or final guidance document**

**FDA deficiency:**
[1] You provided a test report (Appendix C) where you assessed the ability of your bone cement and the predicate to be injected through screws in the spine. In the Specimen Information section of provided test report, you stated the cadaver had non-osteoporotic bone. [2] However, this is not worst-case for your proposed indication, which includes use in osteoporotic bone. Osteoporotic bone is more porous than non-osteoporotic bone

and so is more susceptible to cement extravasation beyond the site of intended administration. [3] Cement extravasation in the spine can cause several safety and effectiveness concerns, including but not limited to, nerve root compression and pulmonary embolisms. [4] If you intend to market your device with indications for use in osteoporotic bone, please provide performance data to support this indication. We recommend that you provide a complete test report describing successful delivery of your device through the ABC Spinal System into a void space using cadaveric and/or foam test blocks that are representative of worst-case osteoporotic bone, and that you provide a comparison to the predicate. Results of your testing should include an adequate rationale for how the cadaveric and/or foam block testing represents worst-case osteoporotic bone, as defined by the proposed indications for use statement. Alternatively, if you do not intend to market your device in osteoporotic bone, we recommend that you remove the indications that refer to use in osteoporotic bone. *[Relevant to 510(k)s only]*

**Applicant response:**
We have updated the indications for use to remove reference to use in osteoporotic bone. See Appendices 1, 2, and 3 for the updated Indications for Use Statement, 510(k) Summary, and labeling. *[Relevant to 510(k)s only]*

7. **Statement of basis for the deficiency without specific reference to final rule, statute, FDA-recognized consensus standard, or final guidance document**

**FDA deficiency:**
[1] In Section 8 of your premarket submission, you provided results from a precision study for your *in vitro* test. [2] However, this study design did not include a sufficient number of replicates or distribution of hCG concentrations around (and at) the device's designed cutoff. A higher number of replicates and more adequate analyte distribution around (and at) the cutoff are necessary to validate your device's precision performance and [3] to demonstrate your device is substantially equivalent to the predicate, which had a more comprehensive precision study design (with more replicates and better analyte distribution per its publicly-available Decision Summary). [2] Imprecision around your device's designed cutoff increases the risk of erroneous test results (i.e., false positive and/or false negative results) [3] which, in your intended use population, could place mothers or their fetuses at increased risk due to incorrect patient management. [4] Therefore, please provide results from a new precision study where you evaluate a sufficient number of replicates and distribution of hCG concentrations (while incorporating other relevant contributors to imprecision such as lots and operators), equivalent to what was provided to support performance of the predicate. If the precision performance of your device is different than that of other legally marketed devices, such that your device could have an increased risk of false positive or false negative results, please provide information to show that you have adequately mitigated this risk. *[Relevant to in vitro diagnostic 510(k)s only]*

**Applicant response:**
We have included updated precision study results (Section B) and updated labeling (Section E) to address the Agency's concern about a sufficient number of replicates and

adequate distribution of hCG concentrations around (and at) the cutoff. We have also included a comparison of these results to the predicate and other legally marketed hCG devices (in Table 2 below). *[Relevant to in vitro diagnostic 510(k)s only]*

8. **Statement of basis for the deficiency without specific reference to final rule, statute, FDA-recognized consensus standard, or final guidance document**

**FDA deficiency:**
[1] For the primary safety and effectiveness endpoints in your submitted study (Appendix D), you presented subgroup analyses according to several characteristics such as clinical severity, physiologic location, and sex of the subject. [2] However, you did not present subgroup analyses according to comorbid conditions (e.g., history of hypertension, smoking) or concomitant medication use (e.g., steroids). It is important to stratify the data according to these heterogeneous characteristics [3] in order to understand whether the safety and effectiveness of your device and treatment is comparable between these different subgroups. For example, if the risks of treatment with your device are increased for one specific comorbid condition, then this information would be valuable to the physician in assessing whether to treat that patient or not, or to properly inform the patient of these increased risks. [4] Therefore, please perform additional subgroup analyses of your primary safety and effectiveness endpoints according to comorbid conditions and concomitant clinically relevant medications. *[Relevant to all marketing applications]*

**Applicant response:**
In response to FDA's request, we have reanalyzed our primary endpoint based on the comorbidities observed in our trial in Section 3 of this response. This analysis evaluated the most frequently observed comorbidities and their relative impact on the primary safety and effectiveness endpoints. Additionally, this subgroup analysis has been added to the draft labeling to help better inform clinicians when using this device. Please refer to Section 3 of our response for additional details regarding this analysis. *[Relevant to all marketing applications]*