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

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Guidance for Industry and Food and Drug Administration Staff

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

Center for Devices and Radiological Health
Center for Biologics Evaluation and Research

Preface

Public Comment

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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 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 standard(s) referenced in this document, see the FDA Recognized Consensus Standards Database Web site at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required. 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 authorizations (e.g., PMA approval, 510(k) clearance, HDE approval, and De Novo granting order). 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 e-mail 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," (https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM341948.pdf), "FDA and Industry Actions on Premarket Notification (510(k)) Submissions: Effect on FDA Review Clock and Goals," (http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089738.pdf), "FDA and Industry Actions on Premarket Approval Applications (PMAs): Effect on FDA Review Clock and Goals," (http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089734.pdf), and "FDA and Industry Actions on De Novo Requests: Effect on FDA Review Clock and Goals" (https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM576305.pdf).

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."[1]

- "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."[2]

- 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."[3]

- "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."[4]

- 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.[5]

- The Least Burdensome Provisions do not change the standards for premarket approval or substantial equivalence.[6]

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[1] See FD&C Act, Section 513(i)(1)(D)(i).
[2] See FD&C Act, Section 513(a)(3)(D)(ii).
[3] See FD&C Act, Section 515(c)(5)(A).
[4] See FD&C Act, Section 515(c)(5)(C).
[5] See FD&C Act, Sections 513(i)(1)(D)(ii), 513(a)(3)(D)(iii), and 515(c)(5)(B).
[6] See FD&C Act, Sections 513(i)(1)(D)(iii), 513(a)(3)(D)(iv), and 515(c)(5)(D).

Information about specific approaches to the Least Burdensome Provisions are detailed in the FDA guidance document "The Least Burdensome Provisions of the FDA Modernization Act of 1997: Concept and Principles" (http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm085999.pdf). 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)]" (https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM284443.pdf).

In the Medical Device User Fee Amendments of 2017 (MDUFA IV) Commitment Letter from the Secretary of Health and Human Services to Congress,[7] FDA committed to update this guidance document to indicate that all "deficiency letters will 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. All 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 De Novo 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 are included in Appendix A. Examples of different approaches to respond to FDA deficiencies are included in Appendix B.

IV. Deficiency letters in marketing applications

A. Guiding principles

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

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

1. Information unrelated to the regulatory 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.

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

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

6. FDA may also include additional considerations that are suggestions, recommendations, or requests that are not expected to preclude a favorable decision on the marketing application. 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. Acknowledgment of the information submitted by the applicant, including references to sections, page numbers, or tables where appropriate.

2. Explanation of why the current information does not adequately address the issue (i.e., what is deficient).

3. Explanation of the request's relevance to the PMA RASE determination, 510(k) SE determination, HDE safety and probable benefit determination, or De Novo classification determination, including, where appropriate, reference to an applicable section of a final rule, final guidance, and/or an FDA-recognized standard (unless the entire or most of the document is applicable). 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.

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

FDA review staff may 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 IV Commitment Letter, all deficiency letters will undergo supervisory review prior to issuance to ensure the deficiencies cited are relevant to the marketing authorization decision and include the four elements described above in Section IV.B of this guidance. 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," (http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089738.pdf), "FDA and Industry Actions on Premarket Approval Applications (PMAs): Effect on FDA Review Clock and Goals," (http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089734.pdf), and "FDA and Industry Actions on De Novo Requests: Effect on

FDA Review Clock and Goals" (https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM576305.pdf).

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

1. Restate the identified Agency issue; and

2. Provide one of the following:

    a. the information or data requested;

    b. an explanation why the issue is not relevant to 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 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, refer to the FDA guidance document "Recognition and Use of Consensus Standards" (https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm077295.pdf).

As stated in 2b above, if you believe that the Agency's request is not relevant to the marketing authorization, you should provide a justification in your response to FDA's deficiency letter. If a legally marketed predicate is available to support your argument for 510(k) submissions, 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. 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.

Appendix A. Deficiency examples

The following examples 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 parentheses to demonstrate how each example satisfies the four-part deficiency format approach. FDA does not intend to enumerate each portion of the four-part deficiency format in deficiency letters.

1. **510(k) – scientific issue**

   (1) You provided line data for your prospective study for your *in vitro* test. From the dates listed in the line data for specimen collection and inoculation, it appears that both fresh and frozen samples were tested. (2) However, you did not identify fresh and frozen samples in the line data, nor did you stratify clinical performance by fresh and frozen status. (4) Please update the line data to indicate fresh and frozen status and stratify clinical performance by this parameter (3) so that we may better understand the performance of your test under your proposed conditions of use identified in your draft labeling.

2. **510(k) – reference to FDA-recognized consensus standard**

   (1) You referenced the currently FDA-recognized version of ISO 7886-1 in your submission for your hypodermic syringe and did not include a declaration of conformity. (2) While you have submitted several tests under ISO 7886-1, you did not include a summary of your testing regarding limits for acidity or alkalinity or limits for extractable metals (Clauses 6 and 7). (3) You should demonstrate conformance to Clauses 6 and 7 (or demonstrate substantial equivalence otherwise) because your identified predicate device was determined to be substantially equivalent through ISO 7886-1 conformance. (4) Therefore, please provide the test results from these two tests or provide a declaration of conformity to the methods and acceptance criteria identified in Clauses 6 and 7 of ISO 7886-1, so that FDA may assess whether your performance data support the substantial equivalence of your device to the predicate device.

3. **510(k) – reference to final guidance document**

   (1) You have proposed that your powered muscle stimulator is intended to be used in the home environment by lay users. (2) However, you have only included professional labeling intended for healthcare providers. (3) FDA recommends in our "Guidance on Medical Device Patient Labeling," (https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070801.pdf) that you provide patient labeling for your device since you intend for patients to operate the device. (4) Therefore, please submit patient labeling that explains your device and includes directions for use, study design and results, and any additional relevant information. Please use clear language and terms understandable by the lay person. Please also include a glossary of all relevant medical terms and ensure

that all appropriate contraindications, warnings, and precautions from the professional labeling are conceptually the same, but are rewritten for understanding by the lay person.

4. **De Novo – reference to final guidance document**

   (1) You have provided a technological description for the inflation catheter used in your device; (2) however, you have not described the software used to operate the alarm that illuminates when the pressure is outside of your intended range. (4) Therefore, please provide the software documentation recommended by FDA in the guidance document "Content of Premarket Submissions for Software Contained in Medical Devices" (http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089593.pdf). (3) This documentation is important to verify that your device is operating within safe parameters and that risks to health have been effectively mitigated to support De Novo classification. Based on our interim review, we believe your device has a Major Level of Concern.

5. **De Novo – scientific issue**

   (1) You have included a device description for your ophthalmic surgical device. (2) However, your description does not completely explain your device's design and its functional modules. You did not describe how the device is controlled and operated, and how your device communicates with other devices. (4) Please provide a block diagram that indicates major functional electronic modules of the device, interconnection between these modules, and a detailed description of each functional module. Please ensure that your description also includes communication interfaces with other devices. Please provide this information for both hardware and software interfaces. (3) This information is necessary to understand the functionality of your device and evaluate the adequacy of the tests you have conducted to demonstrate the safety and performance of your device.

6. **PMA – scientific issue**

   (1) You have provided the protocol and test results to request a one-year shelf life for your intragastric balloon system. (2) However, FDA is concerned that the test article used for this testing is not representative of the final finished device because you have made several design changes to your device since this testing was completed. (3) The Agency has determined that your design changes are likely to impact the performance of your device. Therefore, your shelf life performance testing does not support your identified one-year shelf life. (4) Please provide the protocol and test reports that include performance testing on the final finished device after aging to support your identified one-year shelf life for the product.

7. **PMA – reference to FDA-recognized consensus standard**

   (1) You have provided draft labeling that includes the elements outlined in 21 CFR 809.10. This draft labeling indicates that your assay measuring range is from 5-200

µg/mL. (2) Your linearity studies provided in Volume 4 support the high end of this labeling claim, but do not demonstrate acceptable assay precision near 5 µg/mL. Under clinical use, the medical decision point may approach 5 µg/mL. (3) Users of your assay should be aware of its precision at this concentration in order to correctly interpret results. Additionally, you should demonstrate acceptable performance at the lower limit of your claimed measuring range to demonstrate a reasonable assurance of safety and effectiveness. (4) Please either modify your assay measuring range to be consistent with existing supporting data or provide additional data to support your claimed measuring range. To demonstrate performance at 5 µg/mL, you could perform level of quantitation studies according to the currently FDA-recognized version of CLSI EP17: *Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures*, incorporate samples near 5 µg/mL in your precision studies following CLSI EP05: *Evaluation of Precision of Quantitative Measurement Procedures,* or provide an alternative, scientifically valid method to address the Agency's concern at the lower limit of your currently labeled measuring range.

8. **De Novo – reference to final rule**
   (1) You provided draft labeling in your De Novo request for your orthopedic implant system. (2) Your labeling did not include the name and place of business of the manufacturer, packer, or distributor, (3) which is required by 21 CFR 801.1. (4) In your response, please provide updated labeling that includes the name and place of business of the manufacturer, packer, or distributor for your device.

9. **510(k) – reference to final guidance document and FDA-recognized consensus standard**

   (1) You have provided the protocols and results from a cytotoxicity test using your device in its final finished form, as recommended by the FDA guidance document "Use of International Standard ISO 10993-1, 'Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process.'" (2) However, we have identified the following inadequacies in your testing:

   a. The currently FDA-recognized version of ISO 10993-12 recommends the use of surface area to determine the amount of device included in the extract, with weight being used only for devices or components where the surface area cannot be calculated. (3) We are concerned that use of weight instead of surface area may result in a false negative finding from the study (i.e., a negative finding may occur as a result of insufficient sample being present in the test system). (4) Please provide information to demonstrate that the use of weight to determine extraction ratio has an equivalent or greater amount of test article as compared to use of surface area.

   b. Your extract was described as having particulates following the extraction period. (4) Please provide a justification that the presence of particulates in the extract is (3) not indicative of problems with your finished device, and/or inappropriate extraction conditions that may invalidate the findings of the study.

Information regarding the chemistry of the product may be helpful to your response.

If you cannot provide an adequate rationale, FDA recommends that you complete new cytotoxicity testing using a sample preparation approach consistent with the surface area recommendations in the currently FDA-recognized version of ISO 10993-12.

Appendix B. Deficiency response examples

The following examples are only intended to illustrate the principles and recommendations discussed in this guidance document. Some of the examples include justifications in lieu of the requested information. These would not necessarily be considered adequate to support marketing authorization, but are shown as potential alternative approaches.

1. **510(k) deficiency response**

   FDA deficiency:
   You provided line data for your prospective study for your *in vitro* test. From the dates listed in the line data for specimen collection and inoculation, it appears that both fresh and frozen samples were tested. However, you did not identify fresh and frozen samples in the line data, nor did you stratify clinical performance by fresh and frozen status. Please update the line data to indicate fresh and frozen status and stratify clinical performance by this parameter so that we may better understand the performance of your test under your proposed conditions of use identified in your draft labeling.

   Applicant response:
   We have included stratified results and updated labeling to address the Agency's concern about performance with fresh and frozen specimens. We have included our results in Appendix 1 with updated labeling in Appendix 2 of our response.

2. **510(k) deficiency response**

   FDA deficiency:
   You referenced the currently FDA-recognized version of ISO 7886-1 in your submission for your hypodermic syringe and did not include a declaration of conformity. While you have submitted several tests under ISO 7886-1, you did not include a summary of your testing regarding limits for acidity or alkalinity or limits for extractable metals (Clauses 6 and 7). You should demonstrate conformance to Clauses 6 and 7 (or demonstrate substantial equivalence otherwise) because your identified predicate device was determined to be substantially equivalent through ISO 7886-1 conformance. Therefore, please provide the test results from these two tests or provide a declaration of conformity to the methods and acceptance criteria identified in Clauses 6 and 7 of ISO 7886-1, so that FDA may assess whether your performance data support the substantial equivalence of your device to the predicate device.

   Applicant response:
   We did not include this testing because the purpose of this 510(k) is to modify our own predicate device. We have not changed any materials in our syringe. Therefore, the test results from the predicate device to address limits for acidity and alkalinity and limits for extractable metals are still valid.

3. **510(k) deficiency response**

FDA deficiency:
You have proposed that your powered muscle stimulator is intended to be used in the home environment by lay users. However, you have only included professional labeling intended for healthcare providers. FDA recommends in our "Guidance on Medical Device Patient Labeling," (https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070801.pdf) that you provide patient labeling for your device since you intend for patients to operate the device. Therefore, please submit patient labeling that explains your device and includes directions for use, study design and results, and any additional relevant information. Please use clear language and terms understandable by the lay person. Please also include a glossary of all relevant medical terms and ensure that all appropriate contraindications, warnings, and precautions from the professional labeling are conceptually the same, but are rewritten for understanding by the lay person.

Applicant response:
We have included draft patient labeling in Section 5 of our response. Our draft patient labeling addresses the recommendations outlined in the FDA "Guidance on Medical Device Patient Labeling."

4. **De Novo deficiency response**

FDA deficiency:
You have provided a technological description for the inflation catheter used in your device; however, you have not described the software used to operate the alarm that illuminates when the pressure is outside of your intended range. Therefore, please provide the software documentation recommended by FDA in the guidance document "Content of Premarket Submissions for Software Contained in Medical Devices" (http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089593.pdf). This documentation is important to verify that your device is operating within safe parameters and that risks to health have been effectively mitigated to support De Novo classification. Based on our interim review, we believe your device has a Major Level of Concern.

Applicant response:
The light alarm included in our inflation catheter does not have software. Our pressure gauge is connected to a resistor-based system that powers the light-based alarm. Therefore, FDA's request is not relevant to this marketing application. For this reason, we have not included any software information in our response. We have included a more detailed device description in Section 3 of our response that includes engineering schematics of the alarm system.

5. **De Novo deficiency response**

FDA deficiency:
You have included a device description for your ophthalmic surgical device. However, your description does not completely explain your device's design and its functional

modules. You did not describe how the device is controlled and, operated, and how your device communicates with other devices. Please provide a block diagram that indicates major functional electronic modules of the device, interconnection between these modules, and a detailed description of each functional module. Please ensure that your description also includes communication interfaces with other devices. Please provide this information for both hardware and software interfaces. This information is necessary to understand the functionality of your device and evaluate the adequacy of the tests you have conducted to demonstrate the safety and performance of your device.

Applicant response:
In our response, we have included an updated device description that addresses each of the Agency's above requests in Section 2. Section 2.1 includes information for the control and operation of our device by the user. Section 2.2 includes graphics describing the communication with compatible devices, block diagrams, electronic modules, and the connection between all electronic modules. We have included a description of these graphics in Section 2.1. We trust that this information will allow the Agency to complete its review.

6. **PMA deficiency response**

FDA deficiency:
You have provided the protocol and test results to request a one-year shelf life for your intragastric balloon system. However, FDA is concerned that the test article used for this testing is not representative of the final finished device because you have made several design changes to your device since this testing was completed. The Agency has determined that your design changes are likely to impact the performance of your device. Therefore, your shelf life performance testing does not support your identified one-year shelf life. Please provide the protocol and test reports that include performance testing on the final finished device after aging to support your identified one-year shelf life for the product.

Applicant response:
We have used the same aging protocol from our original submission. We have included test results that include performance testing of the modified device after accelerated aging. We believe the results that we provided support our one-year shelf life claim.

7. **PMA deficiency response**

FDA deficiency:
You have provided draft labeling that includes the elements outlined in 21 CFR 809.10. This draft labeling indicates that your assay measuring range is from 5-200 µg/mL. Your linearity studies provided in Volume 4 support the high end of this labeling claim, but do not demonstrate acceptable assay precision near 5 µg/mL. Under clinical use, the medical decision point may approach 5 µg/mL. Users of your assay should be aware of its precision at this concentration in order to correctly interpret results. Additionally, you should demonstrate acceptable performance at the lower limit of your claimed measuring range to

demonstrate a reasonable assurance of safety and effectiveness. Please either modify your assay measuring range to be consistent with existing supporting data or provide additional data to support your claimed measuring range. To demonstrate performance at 5 µg/mL, you could perform level of quantitation studies according to the currently FDA-recognized version of CLSI EP17: *Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures*, incorporate samples near 5 µg/mL in your precision studies following CLSI EP05: *Evaluation of Precision of Quantitative Measurement Procedures,* or provide an alternative, scientifically valid method to address the Agency's concern at the lower limit of your currently labeled measuring range.

Applicant response:
We have included the test results from a level of quantitation study according to CLSI EP17. We have included the complete test report in Amendment 2 – Volume 6.

8. De Novo deficiency response

FDA deficiency:
You provided draft labeling in your De Novo Request for your orthopedic implant system. Your labeling did not include the name and place of business of the manufacturer, packer, or distributor, which is required by 21 CFR 801.1. In your response, please provide updated labeling that includes the name and place of business of the manufacturer, packer, or distributor for your device.

Applicant response:
We have included updated draft labeling in Section 3 of our response to include the name and place of business for our distributor.

9. 510(k) deficiency response

FDA deficiency:
You have provided the protocols and results from a cytotoxicity test using your device in its final finished form, as recommended by the FDA guidance document "Use of International Standard ISO 10993-1, 'Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process.'" However, we have identified the following inadequacies with your testing:

a. The currently FDA-recognized version of ISO 10993-12 recommends the use of surface area to determine the amount of device included in the extract, with weight being used only for devices or components where the surface area cannot be calculated. We are concerned that use of weight instead of surface area may result in a false negative finding from the study (i.e., a negative finding may occur as a result of insufficient sample being present in the test system). Please provide information to demonstrate that the use of weight to determine extraction ratio has an equivalent or greater amount of test article as compared to use of surface area.

b. Your extract was described as having particulates following the extraction period. Please provide a justification that the presence of particulates in the extract is not indicative of problems with your finished device, and/or inappropriate extraction conditions that may invalidate the findings of the study. Information regarding the chemistry of the product may be helpful to your response.

If you cannot provide an adequate rationale, FDA recommends that you complete new cytotoxicity testing using a sample preparation approach consistent with the surface area recommendations in the currently FDA-recognized version of ISO 10993-12.

Applicant response:
Regarding the Agency's two concerns:

a. We have calculated our device's surface area. Based on our attachment in Section 2.1 of our response, the use of device weight resulted in use of two times more device than if surface area had been used for sample preparation. Therefore, our cytotoxicity test was more sensitive than required by the ISO 10993-12 standard.

b. The particulates present in our extract are an artifact from the cutting process. Our device is manufactured from fibrous material that unravels after cutting and agitation during the extraction process. In Section 2.2 of our response, we have included photographs and chemical characterization information to support our statement that our extraction was valid.

We believe that our existing cytotoxicity results are adequate to demonstrate the biocompatibility of our device for its intended use.