Suggested Format for Developing and Responding to Deficiencies in Accordance with the Least Burdensome Provisions of FDAMA; Final Guidance for Industry and FDA Staff

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Preface

Public Comment

Comments and suggestions may be submitted at any time for Agency consideration to Dockets Management Branch, Division of Management Systems and Policy, Office of Human Resources and Management Services, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD, 20852. When submitting comments, please refer to the exact title of this guidance document. Comments may not be acted upon by the Agency until the document is next revised or updated.

For questions regarding the use or interpretation of this guidance contact Joanne R. Less, Ph.D. at (301) 594-1190 or email jrl@cdrh.fda.gov.

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Suggested Format for Developing and Responding to Deficiencies in Accordance with the Least Burdensome Provisions of FDAMA

This document is intended to provide guidance. It represents the Agency's current thinking on the above. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

Introduction

This guidance document consists of two parts. Part I of the document is intended to help FDA reviewers develop direct, concise, and complete deficiencies when requesting additional information from industry regarding an application under review. In Part II of this document, industry is provided with a suggested format for responding to these requests for additional information. Examples of well-constructed deficiencies as well as responses to these requests are provided. Conscientious use of this document by both FDA staff and industry should help to save time, effort, and resources by both parties.

Part I
Suggested Format for Developing Deficiencies In Accordance With the Least Burdensome Provisions of FDAMA

Purpose: This part of the guidance document provides reviewers with a suggested format for developing deficiencies in accordance with the least burdensome provisions of FDAMA. It is intended to help reviewers develop deficiencies that are direct, concise, and complete, thus ensuring a more effective use of reviewers' and sponsors' time, effort, and resources.

Background: In accordance with the Least Burdensome Concept and Principles document[1], only information, which may include data, that is necessary to make a PMA determination of "reasonable assurance of safety and effectiveness" or a 510(k) determination of "substantial equivalence" should be requested by FDA in its review of an application. The Least Burdensome guidance document also recommends that deficiencies should be divided into minor and major issues. Minor deficiencies should be resolved by phone, fax, or e-mail, whenever possible. These are appropriate alternate means of communication that should be utilized as long

[1] "The Least Burdensome Provisions of the FDA Modernization Act of 1997: Concept and Principles." Released for comment on March 20, 2000. (www.fda.gov/cdrh/modact/leastb.html)

as the confidentiality of the information is assured and the information being collected would not affect the review clock. On the other hand, deficiency letters should be used to address the more complicated and complex issues (i.e., major deficiencies). It may be necessary to include minor deficiencies in these letters if they remain unresolved at the time the major deficiencies are being identified to the firm.

Deficiency Development (Four-Part Approach): As stated above, an effective deficiency should be direct, concise, and complete. The recommended method of writing an effective deficiency is to utilize a four-part approach which consists of the following elements:

1. Clearly identify the specific issue or question;
2. Acknowledge the information submitted and why the information provided did not adequately address the issue;
3. Establish the relevance of the request to the PMA determination of "reasonable assurance of safety and effectiveness" or a 510(k) determination of "substantial equivalence;" and
4. Request the necessary additional information needed to adequately address the issue and, when possible, suggest alternate ways of satisfying the issue.

The following are examples of deficiencies that utilize the four-part method:

PMA Deficiency Example -- Determination of Reasonable Assurance of Safety and Effectiveness

> (1) According to your Investigational Plan, your device is intended to fuse a bone fracture by the 24-month follow-up assessment. (2) You reported that 55% of the study subjects had been followed for 24-months. We are concerned that a meaningful statistical analysis can not be conducted on this study cohort. (3) To thoroughly evaluate the effectiveness of your investigational device, the data set should be complete enough to have sufficient statistical power when compared to the control group. (4) Please continue to follow your study subjects until you have sufficient statistical power at the 24-month follow-up point.

510(K) Deficiency Example -- Determination of Substantial Equivalence

> (1) In your submission, you proposed to use your suture anchor for repairs of the rotator cuff and ankle ligament. (2) You have submitted all of the appropriate testing with the exception of "pull-out" testing for the anchor. We believe that this testing is needed in order to fully characterize the performance of the device. (3) "Pull-out" testing will help to ensure that the device can adequately handle the physiological loading experienced by the rotator cuff and ankle joints. (4) Please provide a complete test report for this testing or justify why it is not necessary.

This four-part approach should be used when requesting additional information from device manufacturers. Deficiencies may vary depending upon the complexity of the issue and, in some cases, on the type of device type; however; in most cases the above format will provide the most direct method of requesting additional information and help to avoid unnecessary delays in the review process.

Part II
Suggested Format for Responding To Deficiencies In Accordance With the Least Burdensome Provisions of FDAMA

Purpose: This part of the guidance document provides industry personnel with a suggested format for responding to deficiencies in accordance with the least burdensome provisions of FDAMA. It is intended to help industry personnel develop responses that are direct, concise and complete, thus ensuring a more effective use of the sponsor's and FDA's time, effort and resources.

Background: In the course of making a PMA determination of "reasonable assurance of safety and effectiveness" or a 510(k) determination of "substantial equivalence," FDA reviewers will, from time to time, determine that more information is required from the sponsor before the decision can be reached. To obtain this additional information, reviewers will develop deficiencies and communicate them to the sponsor. In accordance with the Least Burdensome Concept and Principles document,[2] only information, which may include data, that is necessary to make the appropriate determination should be requested by FDA from the sponsor. This document also recommends that deficiencies be divided into minor and major issues, with minor deficiencies being resolved by phone, fax, or e-mail, whenever possible. These alternative means of communication may be utilized as long as the confidentiality of the information is assured and the information being collected would not affect the review clock. On the other hand, deficiency letters should be developed to address more complicated and complex issues (i.e., major deficiencies). If minor deficiencies remain unresolved at the time the deficiency letter is being drafted, they may be included in the letter.

In Part I of the current document, FDA recommends that its reviewers develop deficiencies using a four-part format consisting of the following:

1. Clearly identify the specific issue or question;
2. Acknowledge the information submitted and why the information provided did not adequately address the issue;
3. Establish the relevance of the request to the PMA determination of "reasonable assurance of safety and effectiveness or to a 510(k) determination of "substantial equivalence;" and
4. Request the necessary additional information needed to adequately address the issue and, when possible, suggest alternate ways of satisfying the issue.

Response to a Deficiency: Upon receipt of a deficiency, the sponsor should make every attempt to respond completely and promptly. The response should:

1. State the Agency issue and
2. Provide one of the following:
   - the information requested;
   - an explanation why the issue is not relevant to substantial equivalence or safety and effectiveness or
   - alternative information and an explanation of why the information adequately addresses the issue.

In developing a response to a deficiency, industry should first provide an exact copy of the Agency's question to remind the reviewer of the information that had been requested. If the deficiency is a follow-up question to a previous deficiency, inclusion of both the original and follow-up question may be helpful. When providing information requested by a reviewer, if the information is extensive, it should be organized for easy access with a table of contents, list of figures and list of tables. A description or justification of how the information adequately addresses the Agency issue is advisable, unless obvious. When referring to standards in lieu of data, identification of the standard, its revision date, applicable sections, and any deviations from the standard should be provided.

If the sponsor believes that the request is not relevant to the regulatory decision being made, the sponsor should explain why. If a legally marketed predicate is available to support this argument, the sponsor should also reference the 510(k) for the predicate.

Finally, in formulating its response, the sponsor may consider suggesting alternate approaches to optimize the time, effort and cost of reaching resolution of the issue within the law and regulations. This could include alternative types of bench testing, proposing non-clinical testing in lieu of clinical testing, the use of standards, etc. It should be noted, however, that whatever approach is taken to address the issue, only information relevant to the decision should be provided.

Example #1 - PMA Deficiency and Response

FDA Deficiency:

(1) According to your Investigational Plan, your device is intended to fuse a bone fracture by the 24-month follow-up assessment. (2) You reported that 55% of the study subjects had been followed for 24-months. We are concerned that a meaningful statistical analysis can not be conducted on this study cohort. (3)To thoroughly evaluate the effectiveness of your investigational device, the data set should be complete enough to have sufficient statistical power when compared to the control group. (4) Please continue to follow your study subjects until you have sufficient statistical power at the 24-month follow-up point.

Industry Response:

FDA requested that additional study subjects be evaluated at 24 months to ensure a meaningful statistical analysis at the 24-month follow-up point. To date, 30 additional study subjects have reached the 24-month follow-up assessment, bringing to 75% the percentage of study subjects that have been evaluated at 24 months. Please find on the following pages: a) an analysis of the 24-month data representing 75% of the study subjects, and b) a rationale supporting 75% as an adequate percentage of the study cohort to allow meaningful analysis.

Example #2 - PMA Deficiency and Response

FDA Deficiency:

(1) In your submission, you state that your device must stand during surgical placement. (2) Data were submitted to support stability; however, no data were presented to demonstrate that the device has adequate strength to withstand bending in a clinical setting. (3) To meet the criteria of reasonable assurance of safety, we believe that additional data are needed to demonstrate that the device will withstand bending during surgical placement. (4) In a clinical setting, please evaluate the strength of the device to withstand bending during surgical placement.

Industry Response:

FDA requested that the strength of our investigational device to withstand bending during surgical placement be evaluated through a clinical trial. The assessment of strength in a clinical trial is burdensome and difficult to assess quantitatively, as its measure may be confounded with other factors. We believe that the strength of the device to withstand bending during surgical placement can be adequately assessed by bench testing. The maximum angle of bending during surgical placement is known. Therefore, testing device strength at this maximum angle is adequate to provide valid evidence of the safety of the device. The methods, data, and statistical analysis showing that strength is adequate are attached.

Example #3 - 510(K) Deficiency and Response

FDA Deficiency:

(1) In your submission, you proposed to use your suture anchor for repairs of the rotator cuff and ankle ligament. (2) You have submitted all of the appropriate testing with the exception of "pull-out" testing for the anchor. We believe that this testing is needed in order to fully characterize the performance of the device. (3) "Pull-out" testing will help to ensure that the device can adequately handle the physiological loading experienced by the rotator cuff and ankle joints. (4) Please provide a complete test report for this testing or justify why it is not necessary.

Industry Response:

FDA requested a complete test report for “pull-out” testing of the suture anchor. Please find on the following pages a test report for this testing of the anchor, which had been performed to support use of the device for anterior shoulder reconstruction. Because the physiological loads in the rotator cuff and ankle ligament are well known and fall within the loads tested for the shoulder, we believe that this testing adequately addresses your request.