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Guidance for Industry and FDA Staff - Procedures for Handling Post-Approval Studies Imposed by PMA Order

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Preface

Public Comment

Written comments and suggestions may be submitted at any time for Agency consideration to the Division of Dockets Management, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD, 20852. Alternatively, electronic comments may be submitted to http://www.fda.gov/dockets/ecomments.

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.

Additional Copies

Additional copies are available from the Internet at: http://www.fda.gov/cdrh/osb/guidance/1561.html . You may also send an e-mail request to dsmica@fda.hhs.gov to receive an electronic copy of the guidance or send a fax request to 240-276-3151 to receive a hard copy. Please use the document number (1561) to identify the guidance you are requesting.

Guidance for Industry and FDA Staff

Procedures for Handling Post-Approval Studies Imposed by PMA Order

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

Introduction

Evaluation of Premarket Approval Applications (PMAs) by the Center for Devices and Radiological Health (CDRH or Center) is a multi-step process in which the Center evaluates the sponsor's information to reach the final decision on whether a product can be approved . To help assure the continued safety and effectiveness of an approved device, CDRH may require a post-approval study (also referred to as Condition of Approval or Post-Approval studies) under 21 CFR 814.82(a)(2), which states:

Post-approval requirements may include as a condition to approval of the device: Continuing evaluation and periodic reporting on the safety, effectiveness, and reliability of the device for its intended use. FDA will state in the PMA approval order the reason or purpose for such requirement and the number of patients to be evaluated and the reports required to be submitted.

Congress recognized the value of postmarket controls in the Food and Drug Administration Modernization Act of 1997 (FDAMA), which added section 513(a)(3)(C) to the Act (21 USC 360c(a)(3)(C)). Section 513(a)(3)(C) provides:

In making a determination of a reasonable assurance of the effectiveness of a device for which an application under section 515 has been submitted, the Secretary shall consider whether the extent of data that otherwise would be required for approval of the application with respect to effectiveness can be reduced through reliance on postmarket controls.

Our goal in this guidance is to provide recommendations to sponsors and CDRH staff on expectations concerning format, content, and review of reports related to post-approval

studies imposed by PMA order to help ensure that the studies are conducted effectively and efficiently, and in the least burdensome manner. Although some post-approval studies may involve animal or laboratory bench studies, the recommendations in this guidance focus on clinical post-approval studies. We intend for these recommendations to improve post-approval studies by:

- helping the Center and sponsors ensure consistency in post-approval submissions;
- helping all stakeholders to easily and quickly identify and track post-approval studies;
- enhancing sponsor and CDRH discussions on mutually understood study objectives;
- facilitating timely discourse on study issues and challenges; and
- providing opportunities to resolve issues.

In sum, these improvements are intended to enhance information about marketed devices by ensuring that appropriate post-approval studies are efficiently initiated, conducted, completed, and reviewed.

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 guidances means that something is suggested or recommended, but not required.

The Least Burdensome Approach

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

Background

The last few years have seen more attention focused on post-approval studies for FDA-regulated products. A 1996 Health and Human Services Office of Inspector General (OIG) study questioned the effectiveness of the Center for Drug Evaluation and Research's (CDER) ability to track postmarketing studies[1]. In 1997, FDAMA imposed certain requirements on postmarket studies of drugs (section 506B (21 U.S.C. 356b)). In response, CDER and the Center for Biological Evaluation and Research (CBER) now post on CDER's website http://www.accessdata.fda.gov/scripts/cder/pmc/index.cfm the

status of certain post marketing studies. In 2005, the Institute of Medicine (IOM) completed a study titled Safe Medical Devices for Children. Among its recommendations, the IOM urged FDA to establish a system for monitoring and publicly reporting the status of postmarket study commitments involving medical devices.

CDRH also initiated an internal review to evaluate its ability to monitor post-approval studies. As a result of that review we have:

- expanded consultation between the Office of Device Evaluation (ODE), Office of In-vitro Diagnostic Device Evaluation and Safety (OIVD), and the Office of Surveillance and Biometrics (OSB) on designing post-approval studies;
- developed a new post-approval study electronic tracking system;
- shifted the responsibility for monitoring the progress and results of post-approval studies from the premarket staff, ODE, to the postmarket staff, OSB;
- established a CDRH work group staffed with premarket and postmarket reviewers to evaluate and recommend methods to improve the quality and completion of post-approval studies;
- determined appropriate public notification and enforcement options concerning post-approval studies; and
- increased focus on inspections to assess compliance with the post-approval study agreement, protocol adherence, subject protection, and data integrity.

These actions are intended to ensure that:

- sponsors produce post-approval studies that use good science and high quality methodology in the study design;
- sponsors provide study results at agreed-upon intervals;
- CDRH provides timely and accurate notification to sponsors regarding their study status; and
- CDRH provides appropriate public notification of study information and, when the legal criteria are met, undertakes actions such as withdrawal proceedings in accordance with section 515(e) of the Act (21 USC 360e(e)) or civil money penalties under 303(f) of the Act (21 USC 333(f)).

Purpose of the Guidance

The guidance has two purposes. First, it is designed to aid sponsors who are subject to clinical post-approval study requirements imposed by PMA order by providing specific recommendations on the information they should include when submitting their post-approval study results.

Second, the guidance is intended to increase the transparency of CDRH's approach to post-approval study requirements. The guidance discusses CDRH's plan to inform stakeholders of the status of post-approval studies by posting the status on the Internet.[2] In addition, the guidance discusses opportunities for sponsors and CDRH staff to present the status of post-approval studies during the public meetings of the Advisory Panels that

may have recommended approving the device with a condition that the sponsor conduct a post-approval study.

Definitions of Terms Used in Reporting Post-Approval Studies

We recommend that in reporting the status of post-approval studies sponsors understand and use the following terms:

Post-Approval Study is a clinical study or other investigation required in the PMA approval order to gather specific information to address precise study objectives about an approved medical device.

Post-Approval Study Commitment is an agreement by the sponsor, and confirmed by FDA in writing, to conduct one or more post-approval studies. Completion of these studies will fulfill that post-approval study commitment.

Interim Post-Approval Study Status Report is a written report to CDRH on the status of the post-approval study prior to its completion. Unless otherwise specified in the PMA approval order, the Interim Post-Approval Study Status Report will usually be submitted every 6 months for the first 2 years of the study and annually thereafter until the time the Final Post-Approval Study Report has been submitted.

Final Post-Approval Study Report is a written report based on the terminated study or the final results of the agreed upon and completed post-approval study. The Final Post-Approval Study Report should be submitted no later than three (3) months after study completion.

You should use one of the terms below to describe the status of the protocol or study:

- Protocol Pending: FDA has not approved the study protocol and it has been less than 6 months since the approval of the PMA.
- Protocol Overdue: FDA has not approved the study protocol and it has been 6 months or more since the approval of the PMA
- Study Pending : The protocol has been approved but the study has not begun (i.e., no subjects have been enrolled), and the projected date for completing patient accrual has not passed.
- Study On-time : The study is proceeding according to, or is ahead of, the agreed upon schedule .
- Study Overdue: The study has not been initiated by the projected date for completion of patient enrollment or the study is behind the agreed upon schedule.
- Study Terminated : FDA granted an early termination of the study because the study is either no longer feasible or would no longer provide useful information.
- Study Completed: FDA has reviewed the Final Post-Approval Study Report and determined that the study fulfills the commitment.

Upon receipt of study status reports, the FDA will determine the report status based on the agreed upon schedule using these terms:

- Report On- time : FDA has received the scheduled Interim or Final Post-Approval Study Status Report by the due date.
- Report Overdue : FDA has not received the Interim or Final Post-Approval Study Status Report by the due date.
- Report Overdue/Received: FDA has received the Interim or Final Post-Approval Study Status Report, although past the due date.
- Final Post-Approval Study Report Submitted : The study has been concluded or terminated, and the Final Post-Approval Study Report has been submitted.

These terms will also be used on the FDA web page to describe the study and report status.

When Should Sponsors Submit Post-Approval Study Protocols?

The final protocol for a post-approval study and the schedule for study completion are based upon agreements reached between CDRH and sponsors during the PMA review process. Generally, we will ask sponsors to submit three (3) copies of the protocols prior to PMA approval. Sponsors should submit a separate study protocol for each post-approval study required. If a final protocol is not agreed upon prior to the PMA approval, the sponsor should submit the protocol as a **PMA supplement** within 30 days of the approval date and clearly label it Post-Approval Study Protocol. In addition, sponsors generally will need to submit Interim Post-Approval Study Status Reports, as discussed later in this guidance. FDA intends to act on and respond to a sponsor's protocol submission within 60 calendar days of receipt.

What Will Happen if the Sponsor and CDRH Cannot Agree on a Protocol?

As discussed earlier, we developed this guidance to help facilitate timely discussions with sponsors on study issues and challenges. We believe that early and on-going interactions with sponsors will afford the optimal opportunities to agree on protocols or other study issues and will be the primary method for resolving any issues. The failure to establish an agreed-upon protocol may result in the Agency using its authority to order postmarket surveillance under section 522 of the act (21 USC 360l; see also 21 CFR Part 822).

What Will Happen if the Sponsor Fails to Complete Post-Approval Studies?

If a sponsor does not comply with post-approval study requirements, other actions may be necessary. In appropriate instances, the Agency has authority to order postmarket surveillance under section 522 of the act (21 CFR Part 822) and, where the legal criteria are met, to withdraw approval of the PMA under section 515(e) of the act (21 CFR 814.46(a)). In addition, a significant or knowing failure to report information about a post-approval study, OR where such failure constitutes a risk to public health, may result in FDA initiating a civil money penalties action.

What Should the Interim Post-Approval Study Status and Final Post-Approval Study Reports Include?

The Center's ability to track and evaluate post-approval studies depends upon the quality and timeliness of information provided by the sponsor. The recommendations in this section are intended to ensure that the reports you submit contain enough information for us to identify the sponsor, product being studied, specific study being conducted, status of the study and the reasons, if any, for delays or failures to complete the study. We believe the data elements below will allow us to provide you with timely and effective feedback.

We recommend that sponsors provide the information listed below as a PMA Post Approval Study Report for each post-approval study submitted under 21 CFR 814.82(a)(2). We recommend the submission of three (3) copies of a PMA Post Approval Study Report that provide the following information, clearly identified and in separate sections:

Section I: General Information : We recommend this section contain the following information:

- Sponsor Name and Information: The name of the individual or entity holding the approved PMA.
    - Company Name/Institution Name
    - Establishment Registration Number
    - Division Name (if applicable)
    - Phone Number (include area code)
    - Fax Number (include area code)
    - Street Address
    - City
    - State/Province
    - Zip/Postal Code
    - Contact name and title
    - Contact e-mail address
- Submission Correspondent Information (if different from Sponsor):
    - Company Name/Institution Name
    - Phone Number (include area code)
    - Fax Number (include area code)
    - Street Address

    - City
    - State/Province
    - Zip/Postal Code
    - Contact name and title
    - Contact e-mail address
- Product Name: The approved product's established name and proprietary name. If the product is distributed under more than one proprietary name, you should include all proprietary names.
- Model Number
- Application Number: The PMA number and supplement number, if any, for which the post-approval commitment was made.
- Date of PMA approval: The date the PMA or PMA supplement was first approved for marketing in the United States. This date will appear on the approval letter for the original application.

Section II: Submission Information : We recommend this section contain the following information:

- Date of Submission
- Data included in this submission (choose one):
    - Clinical Studies,
    - Animal Studies.
- Type of Submission: (Choose one)
    - Interim Post-Approval Study Status Report, or
    - Final Post-Approval Study Report.
    - Response to FDA Correspondence Concerning
        - Deficient Interim Post-Approval Study Status Report,
        - Deficient Final Post-Approval Study Report, or
        - Other Reason (specify).
- Post-Approval Study Status (see Definitions of Terms used in Reporting Post-Approval Studies).
    - Study Pending ,
    - Study On-time ,
    - Study Overdue,
    - Study Terminated,
    - Study Completed.

Section III: Study Information : We recommend this section contain the following information (as applicable):

- Purpose of the study, including study goals and objectives.
- Patient population being studied, including specific illness or condition and whether the study targets subpopulations such as pediatric or geriatrics, the total number of subjects to be studied and schedule of patient follow-up.
- Schedule agreed to by CDRH and the sponsor for conducting the study, including the date CDRH and the sponsor agreed to the schedule. This is the schedule

established by CDRH and you. We recognize that study phases may vary depending on the type and design of the study. However, in conducting a study, certain milestones are common and important to determine the study progress. These are:

  - date of agreed upon study protocol,
  - clinical sites enrollment completion date,
  - patient accrual start date and patient accrual completion date,
  - total patient accrual completion to date,
  - total patient accrual rate to date: You should provide the number of subjects that have been enrolled to date and the total planned enrollment for the study.
  - study targets: percentage of subjects reaching each designated study phase,
  - anticipated study completion date,
  - submission of Interim Post-Approval Study Status Report date, and
  - submission of the Final Post-Approval Study Report date.
- To the extent necessary, you should explain the particular status category.
- Revised schedule, if the study schedule has changed since your last report.
- Explanation for the basis for the revision of the study schedule. You should explain, in detail, the causes for delays and your plan(s) to address the obstacle(s) to continue the study.
- Summary data and interpretation of study results to date.

You should provide the projected dates for phases of the study in the schedule (original or revised) that you submitted to CDRH. In addition, if the post-approval study includes reporting intermediate milestones (e.g., evaluation of surrogate endpoints in a study that also measures clinical benefits), you should include them in the projected schedule. You should use the actual date for any milestones that have been met at the time of the report.

When Should Sponsors Submit Interim Post-Approval Study Status Reports?

Unless otherwise specified in the PMA approval order, you should submit an Interim Post-Approval Study Status Report every 6 months for the first 2 years and annually thereafter from the date of the PMA approval letter or other negotiated starting dates. This should continue until you have submitted the Final Post-Approval Study Report and we have notified you that you have met the commitment.

You should mark the reports as **6-Month Interim Post-Approval Study Status Report, 12-Month Interim Post-Approval Study Status Report, 18-Month Interim Post-Approval Study Status Report, 24-Month Interim Post-Approval Study Status Report**. The 12-Month and 24 Month-Interim Post-Approval Study Status Reports should be submitted separately from your PMA Annual Reports. If you are following a different reporting schedule, you should indicate the appropriate time span on the report cover in bold letters. You should send all reports to:

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20850

How Should Sponsors Submit Final Post-Approval Study Reports?

We recommend that you submit the Final Post-Approval Study Report as a separate report. Your cover letter should prominently identify the submission as **FINAL POST-APPROVAL STUDY REPORT** at the top of the letter and should identify the condition(s) you addressed (i.e., refer to the condition wording and number, if any, used in the approval letter).

How Will CDRH Evaluate Interim Post-Approval Study Status Reports?

CDRH epidemiologists from the Office of Surveillance and Biometrics (OSB) intend to evaluate the Interim Post-Approval Study Status Reports within 60 calendar days of receiving it based on a wide range of criteria. Among these are:

- the completeness of the report content;
- the expected versus the actual progress of the study;
- causes for and solutions to delays in the study progress;
- adherence to agreed upon methodology and reasons for deviations from the methodology; and
- evaluation of the information contained in the reports to assess the performance and postmarket safety and effectiveness of the device.

You should be aware that OSB and ODE will jointly review the Reports when necessary to ensure that the continuing performance of the device is assessed appropriately. If we have questions regarding the data provided in the Report, or if we believe that the data are incomplete or insufficient, we may request additional information, for example, in a deficiency letter. In this instance, you will be asked to respond within a specified time frame.

We will also contact you for clarification if we disagree with your categorization of the status of the study. With this clarification in mind, we will change the status if we believe the data support a different status category.

There may be legitimate circumstances that make it impossible or inappropriate for the sponsor to complete a particular post-approval study. For instance, the firm may have instituted a voluntary withdrawal or recall of the device from the market thereby negating

the need for the study. We strongly recommend that you communicate the issues to CDRH as soon as possible. If we determine that the study cannot be completed as designed but the study objectives remain important, we may terminate the original study and discuss with you establishing a new post-approval study commitment and schedule. If we conclude, however, that you have not met the study commitment required pursuant to 21 CFR 814.82 and you have not provided a scientific justification for doing so, we may also consider whether other options, e.g., postmarket surveillance under section 522 of the Act or, in appropriate cases, enforcement actions including civil money penalties, are necessary.

We recommend that you communicate at the earliest possible time with CDRH if you intend to terminate the study prior to fulfilling the Post-Approval Study commitment.

How Will CDRH Evaluate Final Post-Approval Study Reports?

Your Final Post-Approval Study Report should describe the study and its results and explain how the study fulfills the post-approval study requirement. We will review your Final Post-Approval Study Report and determine whether or not you have satisfied the post-approval study commitment. If we conclude that you have met the study commitment, we will send you a letter informing you that you have satisfied your commitment and you will no longer need to report the status of the study.

When the study outcome affects device labeling, we may request that you file a supplement to the PMA. When this occurs, we will review the submission under established review times for supplements.

What Post-Approval Study Information will be Available to the Public?

In order to be transparent to our stakeholders, including consumers, physicians, and industry, we intend to post information about post-approval study on our website including the status of the on-going studies. We will comply with the requirements of 21 CFR Part 20 on the disclosure of information.

To make information available to the public, we will post the information on the post-approval studies using an Agency website. One type of information will come from the sponsors' submissions (e.g., Application Number, Applicant Name, and Device Name). A second type of information that requires dates will be completed at the appropriate time (e.g., Date PMA Approved, Protocol Accepted Date, Reporting Schedule, Post-Approval Interim Status Report Due Date, FDA Receipt Date, and Date FDA Sent Decision Letter). A third type of information will be based on the knowledge and experience of the FDA personnel involved in reviewing the post-approval study (e.g., Post-Approval Study Description, Status Category, and Comment Section).

The data elements that may be posted are:

- PMA Application Number
- Applicant Name
- Device Name
- Date PMA Approved
- Protocol Approval Date
- Post-Approval Study Description
- Reporting Schedule
- Post-Approval Study Submission Due Date
- FDA Receipt Date
- Date FDA Sent Decision Letter
- Status Category
- Comment Section (helps further explain other parts of the web posting such as clarifying the Status Category).

We will list study information on the FDA Internet website for 1 year following the date of CDRH's letter confirming that the commitment was fulfilled. After that year has passed, we intend to remove the references from the website. This approach is consistent with the FDA policy on CDER and CBER postmarket studies.

Presenting Post-Approval Study Information to CDRH Advisory Panels

We may seek the advice of Advisory Panels when considering the initiation or progress of post-approval studies. These panels are composed of experts outside CDRH who independently review information and make recommendations to us. Public announcement of Advisory Panel Meetings are made at least 30 calendar days prior to the meeting. To assure the Advisory Panel is kept current on the progress of the post-approval studies, we may present or may request that you present the status or outcomes of the studies to the Advisory Panels during their public meetings. Your presentations should contain the information requested in the section of this guidance entitled "What Should the Interim Post-Approval Status Study Reports Include?" Our presentations will include our analysis and evaluation of the post-approval study.

Summary

In summary, this guidance describes how CDRH will monitor post-approval studies imposed by PMA order. CDRH will generally seek agreement on a protocol before imposing a post-approval study by PMA order. Unless agreement is reached on a different schedule, sponsors should expect to submit status reports containing basic information about the study every 6 months for the first 2 years, and annually thereafter. This guidance describes the content of these status reports and CDRH's intention to publish the status of post-approval studies on its web site.

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[1] Postmarketing Studies of Prescription Drugs. Department of Health and Human Services, Office of Inspector General Final Report, May 1996.

[2] As noted earlier, CDER and CBER already provide similar information on their websites.