Guidance for Industry and FDA Staff

Procedures for Handling Post-Approval Studies Imposed by PMA Order

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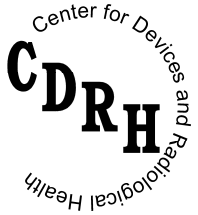

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Division of Epidemiology
Office of Surveillance and Biometrics

Preface

Public Comment

Written comments and suggestions may be submitted at any time for FDA consideration to the Division of Dockets Management, 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 FDA until the document is next revised or updated.

Additional Copies

Additional copies are available from the Internet at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070974.htm. 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 301-847-8149 to receive a hard copy. Please use the document number (1561) to identify the guidance you are requesting.

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

1. Introduction

Evaluation of premarket approval applications (PMAs) by the Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) is a multi-step process in which we evaluate your information to decide if a product can be approved. To help assure the continued safety and effectiveness of an approved device, we may require a post-approval study as a condition of approval under 21 CFR 814.82(a)(2).[1] A post-approval study may be a clinical or non-clinical study required in the PMA approval order and is intended to gather specific information to address questions about the postmarket performance of or experience with an approved medical device.

This guidance document is intended to assist you if you are subject to post-approval study requirements imposed by the PMA order by providing:

- procedural information
- recommendations on the format, content, and review of post-approval submissions
- recommendations applicable to both clinical and non-clinical post-approval studies.

This guidance document also aims to increase the transparency of FDA's approach to post-approval study requirements to stakeholders. Transparency initiatives include posting the status

[1] The focus of this guidance document is on post-approval studies imposed by PMA order. However, most of the information in this guidance document also applies to post-approval studies imposed by humanitarian device exemption (HDE) and product development protocol (PDP) applications.

of post-approval studies on FDA's website or presenting the status during public meetings of the Advisory Panels.

The primary changes from the 2007 version of this guidance document are: (1) revised study status categories that more accurately reflect whether a study is on schedule and the adequacy of the data and (2) recommendations for the content of a post-approval study protocol supplement consistent with our requests of you. We also improved the format of the guidance document. FDA's guidance documents, including this guidance document, do not establish legally enforceable responsibilities. Instead, guidance documents describe FDA'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 FDA guidance documents means that something is suggested or recommended, but not required.

The Least Burdensome Approach

We consider the least burdensome approach in all areas of medical device regulation. This guidance reflects our 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 document.

2. Background

In 2005, the Institute of Medicine (IOM) completed a study, "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.

FDA 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 and OIVD) to the postmarket staff (OSB)

- established an FDA 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 (via the website and advisory meetings) and enforcement options concerning post-approval studies

- increased focus on inspections to assess compliance with the post-approval study agreement, protocol adherence, human subject protection, and data integrity.

These actions aim to ensure:

- 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
- FDA provides timely and accurate notification to sponsors regarding their study status
- FDA 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 Federal Food, Drug, and Cosmetic Act (the act) (21 USC 360e(e)).

3. Post-Approval Study Protocols

Prior to PMA approval, post-approval study protocols and subsequent changes to the approved protocols are submitted and reviewed as amendments to the PMA. However, after PMA approval, post-approval study protocols and subsequent changes are submitted and reviewed as post-approval study supplements to the PMA.

A. Elements to Include in a Post-Approval Study Protocol

FDA recommends you include the following elements in a post-approval study protocol:

- background (e.g., regulatory history, brief description of device, indications for use)
- purpose of study
- study objectives and hypotheses
- study design
- study population (including subject inclusion and exclusion criteria and definition and source of comparator group)
- sample size calculation (statistically justified and based on study hypothesis)
- primary and secondary endpoints (including definitions for study endpoints, success criteria, list of adverse events/complications, standard operating procedures for a determination of relatedness with device and/or the procedure)
- length of follow-up, follow-up schedule, description of baseline and follow-up assessments

- description of data collection procedures (including recruitment plans, enrollment targets, plans to minimize losses to follow-up, follow-up rate targets, quality assurance, and control)
- statistical analysis
- data collection forms, informed consent forms, and IRB approval forms
- reporting requirements for interim and final reports
- study milestones/timeline elements, including:
    - expected date of study initiation
    - expected monthly number of study sites with IRB approvals
    - expected date of initiation of subject enrollment
    - expected number of subjects enrolled per month
    - expected date for subject enrollment completion
    - expected date to complete follow-up of all study participants
    - if applicable, information related to intermediate milestones (e.g., evaluation of surrogate endpoints in a study that also measures clinical benefits).

B. When to Submit a Post-Approval Study Protocol

Ideally, the final protocol for a post-approval study and the schedule for study completion are based on agreements reached between FDA and the sponsor during the PMA review process prior to approval of the PMA. Accordingly, we recommend you submit a proposed post-approval study protocol or, at minimum, post-approval study plans, in the original PMA submission. We also recommend that interactive development of a post-approval study occur concurrently with the review of the premarket data, with the goal of having final agreed-upon protocols by the time of PMA approval.

However, if a final protocol is not agreed upon prior to the PMA approval, the PMA approval order will state that you must submit the post-approval study protocol as a **PMA supplement** within 30 days of the PMA approval date. Your PMA supplement should be clearly labeled as a Post-Approval Study Protocol. If there are multiple protocols being finalized after PMA approval, we recommend each protocol be submitted as a separate PMA supplement. FDA intends to complete the review of a PMA supplement and respond within 60 calendar days.

C. How to Submit Changes to an Approved Post-Approval Study Protocol

If you wish to propose a change to an approved post-approval study protocol, we recommend you submit a **PMA supplement**, clearly labeled as a Post-Approval Study Protocol, for FDA review and approval. If multiple protocols are to be revised, we recommend each be submitted as a separate PMA supplement.

D. What Happens if the Sponsor and FDA Cannot Agree on a Protocol

FDA developed this guidance document to help facilitate timely discussions with sponsors on post-approval study issues and challenges. We believe that early and ongoing interactions will afford optimal opportunities to agree on protocols or other study issues and will be the primary method for resolving any issues. However, if FDA has not approved the study protocol within 6 months after PMA approval, the study status will be categorized as "Protocol Overdue" on FDA's website (see Section 10A).

4. Interim Post-Approval Study Status Reports

An Interim Post-Approval Study Status Report is a written report to FDA on the status of the post-approval study prior to its completion.

A. When and How to Submit an Interim Post-Approval Study Status Report

Unless otherwise specified in the PMA approval order, we recommend you submit the Interim Post-Approval Study Status Report every 6 months for the first 2 years of the study and annually, thereafter, from the date of the PMA approval letter or other negotiated starting date. We recommend you continue this reporting schedule until you have submitted the Final Post-Approval Study Report. We also recommend you indicate the appropriate time span on the interim report cover in bold letters (e.g., **6-Month Interim Post-Approval Study Status Report, 12-Month Interim Post-Approval Study Status Report)**. FDA intends to complete the review of your submission and respond within 60 calendar days.

B. Sponsor's Reporting Status

Upon receipt of the interim report, FDA will determine your reporting status based on the agreed-upon schedule. The reporting status categories appear in the table below.

Status	Definition
Report On Time	FDA has received the scheduled Interim or Final Post-Approval Study Status Report by the due date set in the agreed-upon schedule.
Report Overdue	FDA has not received the Interim or Final Post-Approval Study Status Report by the due date set in the agreed-upon schedule.
Report Overdue/Received	FDA has received the Interim or Final Post-Approval Study Status Report, although receipt was after the due date set in the agreed-upon schedule.

C. Evaluation of Interim Post-Approval Study Status Report

Section 6 provides recommendations on the content and format of the report.

FDA epidemiologists from OSB intend to evaluate the Interim Post-Approval Study Status Report based on a wide range of criteria, including:

- the completeness of the report content

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

OSB will consult with ODE (or OIVD) on the review of a report when necessary to ensure the continuing performance of the device is assessed appropriately.

If we have questions regarding the data provided in the report, or if we believe the data are incomplete or insufficient, we may request additional information through the interactive review process and/or through a deficiency letter.

5. Final Post-Approval Study Reports

A Final Post-Approval Study Report is a written report of a terminated study or a completed post-approval study.

A. When and How to Submit a Final Post-Approval Study Report

We recommend the Final Post-Approval Study Report be submitted no later than three months after study completion, prominently identified with **Final Post-Approval Study Report** at the top of the cover letter. We also recommend you identify the condition of approval for which the report is being submitted (i.e., refer to the condition wording and number, if any, used in the approval letter). FDA intends to complete the review of your submission and respond within 90 calendar days.

B. Sponsor's Reporting Status

As with an interim report, upon receipt of the final report, FDA will determine your reporting status based on the agreed-upon schedule. The reporting status categories are described in the table in Section 4B.

C. Evaluation of Final Post-Approval Study Report

Section 6 provides recommendations on the content and format of the report.

FDA recommends the Final Post-Approval Study Report describe the study methodology and results and explain how the study fulfills the post-approval study requirement. FDA epidemiologists from OSB will review the Final Post-Approval Study Report and determine if you have satisfied the post-approval study commitment. OSB will consult with ODE (or OIVD) on the review of a final report to ensure the continuing performance of the device is assessed appropriately.

If we conclude you have met the study commitment, we will send you a letter stating you have satisfied a particular commitment and will no longer need to report the status of that particular study. When the study outcome affects device labeling, this labeling change will trigger the need for a PMA supplement[2] (21 CFR 814.39). Although ODE (or OIVD) is the lead office for review of labeling supplements, OSB will be consulted on labeling changes resulting from a post-approval study.

6. Content and Format of Interim and Final Post-Approval Study Reports

FDA's ability to adequately track and evaluate post-approval studies depends on the quality and timeliness of information you provide. The recommendations in this section are intended to ensure the reports you submit contain adequate information for us to identify the product being studied, the specific study being conducted, the status of that study, and, if necessary, the reasons for any delays or failures to complete the study.

FDA recommends you provide three copies of a Post-Approval Study Report (interim and final) that includes the information listed below, clearly identified and in separate sections.

A. General Information

FDA recommends this section contain:

- PMA application number and, if applicable, the supplement number for which the post-approval commitment was made

- sponsor name and information (name of the individual or entity holding the approved PMA):
    - company name/institution name
    - street address
    - city
    - state/province
    - ZIP/postal code
    - phone number (include area code)
    - fax number (include area code)
    - contact name and title
    - contact e-mail address

[2] PMA supplements that include only labeling reflecting the results from a post-approval study are logged in as 180-day, no user-fee supplements.

- submission correspondent/contact information (if different from sponsor)[3]:
    - company name/institution name
    - street address
    - city
    - state/province
    - ZIP/postal code
    - phone number (include area code)
    - fax number (include area code)
    - contact name and title
    - contact e-mail address
- date the original PMA or, if applicable, the PMA supplement was approved
- date of post-approval study protocol approval and, if applicable, date(s) of approval of protocol revision(s)
- device trade name(s)
- device model number(s).

B. Submission Information

FDA recommends this section contain:

- date of submission
- data included in this submission (choose one):
    - clinical study
    - laboratory study
    - animal study
- type of submission: (choose one)
    - Interim Post-Approval Study Status Report
    - Final Post-Approval Study Report

[3] If the correspondent/contact information changes for a post-approval study submission, contact one of the project managers referenced on the first page of this guidance document.

- response to FDA correspondence for a deficient report or another reason (specify).

C. Study Information

FDA recommends this section contain (as applicable):

- purpose of the study, including study goals, objectives, and primary and secondary study endpoints
- patient population being studied, including:
  - specific illness or condition
  - whether the study targets subpopulations (e.g., pediatric, geriatric)
  - total number of subjects to be studied
  - schedule of subject follow-up
- begin and end dates of period covered by the report
- date of database closure for the report (should not exceed three months prior to the deadline for submission of report)
- summary of study progress milestones/timeline elements:
  - date of approval of the study protocol
  - number of IRB approvals
  - number of clinical sites enrolled
  - number of clinical sites at which the study was initiated
  - completion date for enrollment of clinical sites
  - number of subjects enrolled (if applicable, this information should be presented for the entire subject population and for each subgroup)
  - subject accrual start date and subject accrual completion date
  - study targets: percentage of subjects reaching each designated study phase
  - comparison of target versus actual enrollment and follow-up
  - anticipated study completion date (i.e., complete follow-up of all study participants)

- a rationale for not meeting the study milestones/timeline specified in the study protocol and a revised study timeline[4] (See Section 7 for details on how FDA will determine Study Status.)

- a revised reporting schedule (e.g., proposing how frequently interim reports are submitted to FDA) with a rationale for the basis of the revision[5]

- subject accountability data stratified by each follow-up timepoint for the entire population and for each subgroup (To limit the potential bias in safety and effectiveness data, you should make every effort to reduce the number of subjects lost-to-follow-up.)

- an explanation for:
    - subjects lost to follow-up, as well as any measure to minimize such future events
    - subject and physician-initiated discontinuations
    - any deaths, including reports from post-mortem examinations

- summary of safety and/or effectiveness data and an interpretation of study results to date.

7. Study Status Determination

After the review of a supplement with a protocol, or of an interim or final report, FDA will determine the status of the study using the categories in the table below.

Status	Definition
Protocol Pending	FDA has not approved the study protocol, and it has been less than 6 months since issuance of the order.
Protocol Overdue	FDA has not approved the study protocol, and it has been 6 months or more since issuance of the order.
Study Pending	This category is used from the time the protocol has been approved to the review of the first report.
Progress Adequate	The study has begun, and the study progress is consistent with the protocol (e.g., meeting enrollment schedule, meeting timeline, adequate follow-up rates, endpoints evaluated).
Progress Inadequate	The study has begun, but the study progress is inconsistent with the protocol (e.g., not meeting enrollment schedule, not meeting timeline, missing timepoint evaluations, poor follow-up rates, not

[4] If a change in the study milestones/timeline could significantly impact the outcome of the post-approval study, then you should submit that revision as part of a PMA supplement for review and approval.

[5] If a change in the reporting schedule could significantly impact the outcome of the post-approval study, then you should submit that revision as part of a PMA supplement for review and approval.

Status	Definition
	all endpoints evaluated).
Completed	The sponsor has fulfilled the condition of approval, and FDA has closed the study. This is a final study status
Terminated	The sponsor has not fulfilled or cannot fulfill the condition of approval (e.g., device is not currently being sold because the device technology is obsolete, study questions are no longer relevant, sponsor withdraws PMA, study cannot answer post-approval study question), all appropriate efforts to fulfill the condition of approval have been exhausted, and FDA has terminated the study. This is a final study status.
Other	The study status does not fit another category (e.g., change in ownership, redesigning device and needing PMA approval prior to use in a post-approval study, pending separate study being used to address condition of approval). This is an interim study status.

8. Where to Submit Post-Approval Study Reports and Supplements

Through July 31, 2009, you should send three copies of all post-approval study reports and supplements to:

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

After July 31st, the new address for the Document Mail Center is as follows:

U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center – WO66 Room G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

9. Failure to Complete a Post-Approval Study

There may be circumstances that make it impossible or inappropriate for you to complete a particular post-approval study. For instance, you may have instituted a voluntary withdrawal or recall of the device from the market, thereby negating the need for the study. You should communicate any such issues to us as soon as possible.

In addition, if FDA determines the study cannot be completed as designed or because of the study data inadequacies, but the study objectives remain important, we may terminate the

original study and discuss establishing a new post-approval study commitment and schedule. We recommend that you initiate early communication with FDA if you intend to terminate the study prior to fulfilling the post-approval study commitment.

If FDA concludes you have not met the post-approval study condition of approval and have not provided a valid scientific justification for doing so, we may take a variety of regulatory actions. Under certain circumstances, we may initiate withdrawal of approval of the PMA under section 515(e) of the act. In appropriate instances, FDA may order postmarket surveillance under section 522 of the act. Note that the failure or refusal of a manufacturer to comply with section 522 is a prohibited act under section 301(q)(1)(C) of the act, 21 U.S.C. 331(q)(1)(C). Further, under section 502(t)(3) of the act, 21 U.S.C. 352(t)(3), a device is misbranded if there is a failure or refusal to comply with any requirement under section 522 of the act. Please note that violations of sections 301(q)(1)(C) or 502(t)(3) may lead to regulatory actions including seizure, injunction, prosecution, or civil money penalties.

10. Public Disclosure of Post-Approval Study Information

A. Website

To increase transparency to our stakeholders, including consumers, physicians, and industry, we will post information about post-approval studies on our website (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/PMA_pas.cfm). This information will be posted in compliance with the requirements of 21 CFR Part 20 on the disclosure of information.

Study details that may be posted include:

- PMA application number
- applicant name
- device name
- medical specialty (e.g., cardiovascular, orthopedic)
- date PMA approved
- post-approval study description
- study name
- protocol approval date
- study population
- study status
- report schedule
- submission due date for report (based on agreed-upon schedule)
- FDA receipt date of report
- status category of report.

We will list study information on FDA's website for one year following the date of FDA's letter confirming all commitments for a given PMA were fulfilled. After that year has passed, we intend to remove the references from the website. This approach is consistent with FDA's policy on CDER and CBER postmarket studies.

B. Advisory Panels

FDA may seek the advice of Advisory Panels when considering the initiation or progress of post-approval studies. These panels are composed of experts outside FDA 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 request that you present the status or outcomes of the studies to the Advisory Panels during their public meetings. We recommend your presentations contain the report contents requested in Section 6. Our presentations will include our analysis and evaluation of the post-approval study.