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Draft – Not for Implementation

Procedures for Handling Post-Approval Studies Imposed by Premarket Approval Application Order

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Draft Guidance for Industry and Food and Drug Administration Staff

This draft guidance document is being distributed for comment purposes only.

Document issued on May 27, 2021.

You should submit comments and suggestions regarding this draft document within 60 calendar days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions about this document, contact OPEQ: Office of Product Evaluation and Quality / OCEA: Office of Clinical Evidence and Analysis / Division of Clinical Science and Quality via email at MandatedStudiesPrograms@fda.hhs.gov.

When final, this guidance will supersede "Procedures for Handling Post-Approval Studies Imposed by PMA Order," issued on June 15, 2009.

FDA U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR DEVICES & RADIOLOGICAL HEALTH

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

Preface

Additional Copies

Additional copies are available from the Internet. You may also send an e-mail request to CDRH-Guidance@fda.hhs.gov to receive a copy of the guidance. Please include the document number 19043 and complete title of the guidance in the request.

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Procedures for Handling Post-Approval Studies Imposed by Premarket Approval Application Order

Draft Guidance for Industry and Food and Drug Administration Staff

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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

Evaluation of premarket approval applications (PMA) 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 whether reasonable assurance of device safety and effectiveness has been demonstrated. To provide reasonable assurance, or the continued assurance, of safety and effectiveness of an approved device, we may require a post-approval study (PAS) as a condition of approval in a PMA approval order under 21 CFR 814.82(a)(2) and 21 CFR 814.82(a)(9).[1] A PAS is usually a clinical or non-clinical study,[2] as specified in the PMA approval order, and is typically intended to gather specific data to address questions about the postmarket performance of or experience with an approved medical device. As described in "Balancing Premarket and Postmarket Data Collection for Devices Subject to Premarket Approval,"[3] FDA may consider it acceptable to collect certain data in the postmarket setting, rather than premarket under certain

[1]Under 21 CFR 814.82(a), FDA may impose post-approval requirements in a PMA approval order or by regulation at the time of approval of the PMA or by regulation subsequent to approval. The focus of this guidance document is on PAS imposed by a PMA approval order at the time of approval of the PMA. However, the recommendations in this guidance document may also apply to PAS imposed at the time of approval of humanitarian device exemption (HDE) applications.

[2] The focus of this guidance is on clinical studies; however, the concepts and principles discussed in this document may also apply to non-clinical PAS.

[3] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/balancing-premarket-and-postmarket-data-collection-devices-subject-premarket-approval.

circumstances when FDA has uncertainty regarding certain benefits or risks of the device, but the degree of uncertainty is acceptable in the context of the overall benefit-risk profile of the device at the time of premarket approval.[4]

The purpose of this draft guidance document, when finalized, is to assist stakeholders with understanding PAS requirements imposed as a condition of PMA approval by providing:

- procedural information;
- recommendations concerning the format, content, and review of PAS-related submissions; and
- updates to the final guidance entitled "Procedures for Handling Post-Approval Studies Imposed by PMA Order"[5] dated June 2009, including:
  - recommendations to help facilitate FDA's review of a PAS protocol in a timely manner;
  - recommendations for study timelines including enrollment milestones and study completion;
  - revised definitions to PAS status categories that we believe better reflect progress of the PAS; and
  - revised FDA review time goals for PAS-related submissions.

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, 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.

II. Background

FDA established an internal tracking system for the PAS Program in 2006,[6] and since that time,

[4] See the following FDA guidance documents for additional information on balancing premarket and postmarket data collection and benefit-risk determinations: "Balancing Premarket and Postmarket Data Collection for Devices Subject to Premarket Approval" (available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/balancing-premarket-and-postmarket-data-collection-devices-subject-premarket-approval); "Breakthrough Devices Program" (available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/breakthrough-devices-program); "Consideration of Uncertainty in Making Benefit-Risk Determinations in Medical Device Premarket Approvals, De Novo Classifications, and Humanitarian Device Exemptions" (available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/consideration-uncertainty-making-benefit-risk-determinations-medical-device-premarket-approvals-de); and "Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications: Guidance for Industry and Food and Drug Administration Staff" (available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/factors-consider-when-making-benefit-risk-determinations-medical-device-premarket-approval-and-de).

[5] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/procedures-handling-post-approval-studies-imposed-pma-order.

[6] *See* Safe Medical Devices for Children, National Academies of Sciences Engineering Medicine, July 18, 2005,

has implemented initiatives to increase transparency, including the establishment of the webpage for the Post-Approval Studies Program Database.[7] The PAS Program Database typically displays the following information for each PAS: general information, general and detailed PAS protocol parameters, interim or final data summary, the sponsor's progress or "study status," and reporting information.

Additionally, CDRH may provide updates on the status of certain PAS requirements during public meetings of a Medical Device Advisory Committee Panel (an "Advisory Panel")[8] and, in the past, has invited sponsors to provide PAS updates to help ensure Advisory Panels are kept current on the progress of a certain PAS.

These steps aim to help ensure that:

- sponsors conduct PAS that use good science and high-quality methodologies in the study design;
- least burdensome[9] approaches are used in the design and conduct of PAS;
- sponsors provide PAS results at intervals specified in the approval order;
- FDA provides timely notification to sponsors regarding their PAS status; and
- FDA posts PAS information publicly and, in situations where the legal criteria are met, undertakes regulatory actions such as withdrawal proceedings in accordance with section 515(e) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 360e(e)) and 21 CFR 814.46.

III. Post-Approval Study Requirements in PMA Approval Orders

When a PAS is required as a condition of approval, the PMA approval order specifies certain information about the requirement (i.e., the reason or purpose for such requirement, the number of patients to be evaluated, and the reports required to be submitted).[10] For each required PAS, FDA intends to describe the following in the PMA approval order: study design, objectives, population, and endpoints to be collected; the length of follow-up and frequency of assessments;

which served as an initial impetus for instituting changes in CDRH's PAS Program. Furthermore, FDA launched the Medical Device Epidemiology Network (MDEpiNet) Initiative in 2010, to develop national/international infrastructure and innovative methodological approaches for conducting robust studies and surveillance, to improve the understanding of medical device safety and effectiveness throughout the device life cycle, through a Public-Private Partnership (PPP) with academia and other stakeholders (www.mdepinet.org). More information on the evolution of the PAS Program can be found here: https://www.fda.gov/medical-devices/post-approval-studies/post-approval-studies-pas-frequently-asked-questions-faq.

[7] https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma_pas.cfm.

[8] *See* FDA Guidance "Procedures for Meetings of the Medical Devices Advisory Committee: Guidance for Industry and Food and Drug Administration Staff," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/procedures-meetings-medical-devices-advisory-committee.

[9] *See* FDA Guidance "Least Burdensome Provisions: Concept and Principles," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/least-burdensome-provisions-concept-and-principles.

[10] See 21 CFR 814.82(a)(2).

and a high-level description of the data analysis plan for the primary endpoints. Generally, FDA also intends to specify PAS timelines in the approval order, including enrollment milestones (or data accrual milestones for a nonclinical study, if applicable), report submission timelines, completion timeline (e.g., complete follow-up and data analyses), and expectations for any additional milestones or submissions, as necessary.

When a PAS is likely to be required as a condition of approval, sponsors and FDA should work together to establish a PAS protocol, enrollment milestones, and study completion timelines prior to PMA approval to help ensure that the PAS achieves its objectives and is completed in a timely manner. Based on FDA's experience with PAS, the enrollment milestones below are recommended in developing your study protocol for clinical studies.[11]

- First subject enrolled within 6 months of the study protocol approval date
- 20% of subjects enrolled within 12 months of the study protocol approval date
- 50% of subjects enrolled within 18 months of the study protocol approval date
- 100% of subjects enrolled within 24 months of the study protocol approval date

IV. Post-Approval Study Protocols

In general, when a PAS is required as a condition of approval, prior approval of the PAS protocol is included as part of the condition. FDA intends to review the PAS protocol interactively with the sponsor during the review of the PMA. After PMA approval, PAS protocols and subsequent changes to approved protocols should be submitted and reviewed as PAS *supplements* to the PMA.[12]

A. Recommended Elements in a Post-Approval Study Protocol

FDA recommends you include the following elements in a PAS protocol:

- background (e.g., device's regulatory history, brief description of device, indications for use)
- purpose of study
- study objectives
- study design
- study population (including subject inclusion and exclusion criteria and definition and source of comparator group)
- enrollment and recruitment plan (including enrollment milestones)
- sample size calculation that is statistically justified and based on study hypothesis, where applicable
- primary and secondary endpoints, when applicable, including definitions for study endpoints and list of adverse events/complications

[11] For non-clinical studies, similar milestones for data accrual can also be used to track study progress.

[12] Even though PMA supplements containing PAS protocols are not considered 180-day supplements for purposes of Medical Device User Fee Amendments (MDUFA) fees, see section 737(4)(C) of the FD&C Act, they should be submitted as 180-day supplements with no user fee.

- procedures for a determination of adverse events/complications relatedness with device and/or the procedure
- length of follow-up, follow-up schedule, plans to minimize losses to follow-up,[13] and follow-up rate targets
- description of baseline and follow-up assessments
- description of data collection procedures (including data management and quality control)
- data analyses and statistical tests planned (such as a statistical analysis plan including interim data release plan, when appropriate, and final data analysis)
- data collection forms, informed consent forms, and Institutional Review Board (IRB) approval forms
- study timelines (see Section III)

B. Post-Approval Study Protocol Review

When a PAS is likely to be required as a condition of approval, FDA intends to review the PAS protocol *interactively* with the sponsor during the review of the PMA and concurrent with the review of the premarket data. FDA's goal is to complete the review of the PAS protocol and establish study enrollment milestones and completion timelines at the time of PMA approval, for inclusion as part of the conditions of approval within the PMA approval order. Accordingly, we recommend that the PMA include a discussion of potential postmarket evaluation needs, a proposed PAS protocol or PAS outline (including objective and general study design, study population, study endpoints, sample size, length of follow-up and frequency of assessments), or the sponsor's rationale as to why a PAS is not needed.

If a PAS protocol has not been developed by the time of PMA approval, the PMA may be approved with a PAS outline. In these circumstances, FDA intends to require, as part of the condition of approval in the PMA approval order, that a PAS protocol must be submitted as a PMA *supplement* within 30 calendar days of the PMA approval date.[14] Your PMA supplement should be clearly labeled as a "PAS Protocol." If there are multiple PAS protocols being finalized after PMA approval, we recommend each protocol be submitted as a separate PMA supplement. FDA strives to finish its review of a study protocol within 60 calendar days of PMA approval. To achieve this, FDA intends to complete the review of a PAS protocol (a PMA supplement) and respond within 30 calendar days of receipt. Sponsors should prioritize resolution of any protocol deficiencies and work interactively with FDA to help ensure that FDA's review of the protocol is completed within 60 calendar days from PMA approval date.

[13] When finalized, we recommend considering the content of the FDA draft guidance entitled, "Patient Engagement in the Design and Conduct of Medical Device Clinical Investigations: Draft Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders" (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-engagement-design-and-conduct-medical-device-clinical-investigations) as a potential approach to minimize losses to follow-up. When final, this draft guidance will represent the current thinking of the FDA on this topic.

[14] See 21 CFR 814.82(a).

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

If you wish to propose a change to an approved PAS protocol after PMA approval, you should submit a PMA *supplement*, clearly labeled as a "PAS Protocol," for FDA review and approval. If multiple PAS protocols are revised, we recommend each be submitted as a separate PMA supplement.

If you are proposing a change in the study enrollment milestones and completion timeline that could delay the completion of the PAS, you should submit that revision as part of PMA supplement with a PAS protocol. The supplement should include a justification for the changes in the study enrollment milestones and completion timeline for FDA review.

D. What Happens if the Sponsor and FDA Cannot Complete the Development of a Post-Approval Study Protocol

FDA intends to facilitate timely discussions with sponsors concerning PAS protocol issues and challenges. We believe that early and ongoing interactions should be the primary method to discuss PAS protocols and resolve any PAS issues. However, if FDA is unable to complete its review of the study protocol within 60 calendar days after PMA approval due to outstanding deficiencies that the sponsor needs to address, we intend for the PAS status to be categorized as "Protocol Overdue" on FDA's PAS Program Database[15] (see Section X for more information on study status).

V. When and How to Submit Post-Approval Study Reports

Per 21 CFR 814.82(a), FDA may impose post-approval requirements in a PMA approval order or by regulation at the time of approval of the PMA or by regulation subsequent to approval. Such requirements may include continuing evaluation and periodic reporting on the safety, effectiveness, and reliability of the device for its intended use.[16] FDA tracks and evaluates the conduct of a PAS through review of study reports submitted to the Agency. An interim report is a written report to FDA on the status of the PAS prior to its completion. Generally, FDA recommends submitting two types of interim reports: "Enrollment Status Report" and "PAS Progress Report." An Enrollment Status Report should provide the progress towards meeting the enrollment milestones per the approval order (see Section III). A PAS Progress Report should describe the status of the PAS prior to its completion, including subject accountability as well as device performance, safety and effectiveness data (See Section VI for additional report content details). A Final PAS Report is a written report of a completed or terminated PAS study.

FDA intends for the PMA approval order to include a submission timeline for PAS reports. The timing of Enrollment Status Reports may be based on the deadlines identified for each

[15] https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma_pas.cfm.
[16] 21 CFR 814.82(a)(2)

enrollment milestone. There may be instances in which the timing for the submission of an Enrollment Status Report coincides with the timing for the submission of an PAS Progress Report. In such instances, a sponsor may decide to submit one report labeled as "Enrollment Status and PAS Progress Report" to address reporting requirements. If study enrollment milestones are missed, FDA may change the timing of your Enrollment Status Reports. Generally, FDA intends to require in the approval order that PAS Progress Reports are to be submitted every six (6) months until subject enrollment has been completed and annually thereafter, and that PAS Progress Reports for PAS without new subject enrollment (e.g., extended follow-up of premarket cohorts) are to be submitted every six (6) months for the first two years of the study and annually, thereafter, from the date of the PMA approval letter or other negotiated starting date. You must follow the reporting schedule, as required by the PMA approval order, until you have submitted the Final PAS Report. Generally, FDA intends to require in the approval order that the Final PAS Report is to be submitted no later than three months after study completion (i.e., last subject's last follow-up date).

To help facilitate and triage review, FDA recommends that the sponsor indicate the type of PAS report and time span on the report cover letter in bold letters (e.g., **Enrollment Status Report**, **6-Month PAS Progress Report**, **12-Month PAS Progress Report, Final PAS Report**). We also recommend that the sponsor identify the condition of approval for which the report is being submitted (i.e., refer to the condition of approval wording and the PAS number if more than one PAS is identified as a condition of approval in the approval order).

FDA requires all applicants to provide one electronic copy (eCopy) of PAS submissions.[17] The eCopy must be accompanied by a single paper copy of your signed cover letter. Submissions should be sent to the current address displayed on the website http://www.fda.gov/cdrhsubmissionaddress.

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

FDA's ability to adequately track and evaluate a PAS depends on the quality and timeliness of the information provided by the sponsor. The recommendations in this section are intended to help ensure the PAS reports that are submitted contain adequate information for FDA to identify the product being studied, the specific study being conducted, the status of that study, and, if applicable, the reasons for any delays or failures to complete the study in accordance with the timelines typically included in the approval order.

FDA recommends that PAS reports (interim and final) include the information listed below, clearly identified, and in separate sections. All reports should contain the data listed below and submitted per the timeline in the approval order.

[17] See Section 745A(b) of the FD&C Act and FDA's eCopy guidance, "eCopy Program for Medical Device Submissions," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/ecopy-program-medical-device-submissions.

A. General Information

FDA recommends all reports include a section that contains the following general information:

- PMA application number and, if applicable, the supplement number for which the PAS requirement was made a condition of approval in the PMA approval order
- Sponsor name and contact 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)
  - Contact name and title
  - Contact e-mail address
- Report correspondent/contact information (if different from sponsor)[18]:
  - Company Name/Institution Name
  - Street Address
  - City
  - State/Province
  - ZIP/Postal Code
  - Phone Number (include area code)
  - Contact name and title
  - Contact e-mail address
- Date of the original PMA or, if applicable, of the PMA supplement approval
- Date of PAS protocol approval and, if applicable, date(s) of approval of protocol revision(s)
- Device trade name(s)
- Device model number(s)
- Date of report submission
- Description of the data included in the report, including:
  - Enrollment data
  - Clinical study data
  - Non-clinical data (e.g., bench/laboratory)
  - Animal study data[19]
  - Other (specify)
- Type of submission:
  - Enrollment Status Report

[18] If the correspondent/contact information changes for a PAS submission, contact MandatedStudiesPrograms@fda.hhs.gov.

[19] FDA supports the principles of the "3Rs," to reduce, refine, and replace animal use in testing when feasible. We encourage sponsors to consult with us if they wish to use a non-animal testing method they believe is suitable, adequate, validated, and feasible. We will consider if such an alternative method could be assessed for equivalency to an animal test method.

- PAS Progress Report
- Final PAS Report
- Response to FDA report deficiency letter
- Other (specify)

B. PAS Enrollment Status Reports

FDA intends to specify the schedule for Enrollment Status Reports within the PMA approval order. Generally, sponsors should submit Enrollment Status Reports until enrollment is completed.[20] The sponsor's Enrollment Status Reports should include sufficient data for FDA to track progress towards the study enrollment milestones as specified in the PMA approval order, including:

- Date of approval of the study protocol
- Start and completion date for clinical site(s) recruitment
- Number of IRB approvals and number of clinical sites at which the study was initiated
- Subject enrollment start date and expected completion date
- Number of subjects enrolled (if applicable, this data should be presented for the entire subject population and for each subgroup)
- Comparison of target versus actual enrollment dates (e.g., first subject enrolled, 20% of subjects enrolled, 50% of subjects enrolled, 100% of subjects enrolled)

C. PAS Progress Reports

FDA recommends PAS Progress Reports include (as applicable):

- Purpose of the study, including study goals, objectives, and primary and secondary study endpoints
- Description of the study population, 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 the sponsor used as cut-off for database for the analysis included in the report (should not exceed three months prior to the deadline for submission of report)
- 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, the sponsor 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

[20] For non-clinical PAS data, accrual milestone reports may be used to track progress.

- any deaths, including reports from post-mortem examinations
- Summary of safety and/or effectiveness data and an interpretation of study results to date

D. Final Post-Approval Study Status Reports

FDA recommends a Final PAS Report includes (as applicable):

- Purpose of the study, including goals, objectives, and primary and secondary endpoints
- Description of the study population, including:
  - specific illness or condition
  - whether the PAS 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 Final PAS Report
- Date of database closure for the Final PAS Report (should not exceed three months prior to the deadline for submission of report)
- Final accountability of enrolled subjects, compared to target
- Final accountability of number of subjects followed, stratified by each follow-up time point for the entire population and for each subgroup
- An explanation for:
  - subjects lost to follow-up
  - subject and physician-initiated discontinuations
  - any deaths, including reports from post-mortem examinations
  - assessment of potential bias introduced by losses to follow-up (e.g., are subjects lost to follow-up different from those that remain under surveillance, is the loss to follow-up differential by study group) and potential impact on interpretation of results
- Summary and interpretation of results
  - final safety/effectiveness findings

VII. Evaluation of Interim Post-Approval Reports

Enrollment Status Report: FDA intends to review Enrollment Status Reports to assess progress towards the study enrollment milestones identified in the PMA approval order (i.e., comparing study enrollment milestones to actual enrollment).

PAS Progress Report: FDA intends to consider several factors when evaluating the PAS Progress Report, including:

- the completeness of the report content (especially in regard to progress towards achieving primary and secondary endpoints and performance goals, or sufficient individual endpoint data to infer progress in the case of composite endpoints);
- whether study enrollment milestones are met (see Section X);
- causes for and solutions to delays in PAS progress or failure to meet enrollment

milestones;
- protocol adherence and reasons for deviations from the methodology; and
- the performance and postmarket safety and effectiveness of the device.

FDA intends to review interim PAS reports within 30 calendar days of submission receipt date. 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 interactively and/or through a deficiency letter. If an interim report includes insufficient data or includes data that raise concerns regarding the safety and/or effectiveness of a device, FDA may take compliance or enforcement action, as appropriate.

VIII. Evaluation of a Final PAS Report

The Final PAS Report should describe the study methodology and results. If the Final PAS Report is for a completed study, it should also explain how the study fulfills the PAS requirement identified in the PMA approval order. If the Final PAS Report is for a terminated study, it should include the data captured prior to termination. See Section VI for additional recommendations on the content and format of PAS reports.

FDA intends to consider multiple factors when evaluating a Final PAS Report, including:

- the completeness of the report content;
- adherence to methodology in the PAS protocol and reasons for deviations from the methodology;
- evaluation of data in the report to assess the performance, safety and effectiveness of the device; and
- evaluation of fulfillment of the condition(s) of approval identified in the PMA approval order.

FDA intends to review final PAS reports within 60 calendar days of submission receipt date. If we have questions regarding the data provided in the Final PAS Report, or if we believe the data are incomplete or insufficient to address the PAS requirement(s), we intend to request additional information through the interactive review process and/or through a deficiency letter.

If we conclude the sponsor has fulfilled the PAS requirement(s), we intend to send the sponsor a letter stating the PAS requirement(s) has been fulfilled. Generally, submission of additional PAS reports to FDA is not necessary after FDA determines that the PAS requirement is satisfied. If the PAS results affect device labeling, the labeling change will generally trigger the need to submit a PMA supplement (21 CFR 814.39).[21]

[21] Even though PMA supplements that include only labeling changes reflecting the results from a PAS are not considered 180-day supplements for purposes of MDUFA fees, they should be submitted as 180-day supplements with no user-fee.

IX. Sponsor's Reporting Status

Upon receipt of an PAS Progress Report or a Final PAS Report, FDA intends to assess the sponsor's reporting status based on the schedule specified in the PMA approval order and post the reporting status on the webpage for the PAS Program Database[22] for each PAS Progress and Final Report submission. The reporting status categories are described in Table 1 below.

Table 1. Reporting Status Categories

Status	Definition
Report on Time	FDA has received the PAS Progress Report or Final PAS Report per the PMA approval order.
Report Overdue	FDA has not received the PAS Progress Report or Final PAS Report per the PMA approval order.
Report Overdue/Received	FDA has received the PAS Progress Report or Final PAS Report, although receipt was after the due date set in the PMA approval order.

X. Study Status

FDA intends to determine the PAS status after reviewing a PMA supplement (i.e., a protocol for a new PAS or modifications to an existing PAS protocol), an Enrollment Status Report, a PAS Progress Report, and a Final PAS Report. Factors in considering the PAS progress and status include, as applicable:

1. Assessing the status of protocol approval;
2. After PAS protocol approval, assessing the following:
    a. Whether the study enrollment milestones are met
    b. Progress with data accrual
    c. Submission of a Final PAS Report

Based on the above, FDA intends to consider the appropriate status category to be posted on the webpage for the PAS Program Database.[23] Refer to Section IV. C for information on how to handle changes to study timelines. Of note, there may be circumstances in which a PAS may be put on a hold temporarily, be redesigned/replaced, or be terminated. A sponsor's progress status is considered based on currently available information and may be revised accordingly based on the availability of new information. Although revisions to the study protocol, enrollment milestones and study completion timelines are sometimes warranted, FDA generally intends to use the original study schedule identified in the PMA approval order to assess the study progress and to designate its status. Each of these status categories are described in Table 2 below.

[22] https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma_pas.cfm
[23] https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma_pas.cfm.

Table 2. PAS Status Category

Status	Definition
Protocol Pending	FDA is reviewing the study protocol, and it has been less than 60 calendar days since issuance of the PMA approval order.
Protocol Overdue	FDA is unable to complete its review of the study protocol due to outstanding deficiencies that the sponsor needs to address, and it has been more than 60 calendar days since issuance of the PMA approval order.
Study Pending	This category is used from the time the PAS protocol has been approved to the initial status assessment based on the data in the first Interim PAS study report.
Ongoing	The study is proceeding according to, or is ahead of, the original study timelines. The FDA considers the study to be ongoing until a Final PAS Report is submitted to the FDA, as long as the activities are proceeding according to the approved study protocol**.**
Delayed	The progression of the study is behind the original study timelines. For example, the enrollment of subjects (or data accrual) may or may not have started but the projected date for completion of that milestone has passed. Delays can occur in any phase of the study, including subject enrollment, analysis of data, or submission of the Final PAS Report to the FDA. While the milestones in the originally approved protocol serve as the basis for defining the study as delayed, each phase of the study will be considered on its own right. If the sponsor has one delayed phase, but gets back on schedule during the next phase, the delayed status will no longer apply.
Completed	The sponsor has fulfilled the post-approval requirement identified in the condition(s) of approval (PAS requirement) in the PMA approval order, and FDA considers the PAS requirement to be satisfied.
Redesigned/Replaced	The sponsor has not fulfilled or cannot fulfill the post-approval requirement identified in the condition(s) of approval (PAS requirement) as originally designed. All reasonable efforts to fulfill the PAS requirement have been exhausted, and FDA has agreed to allow the sponsor to redesign and replace the original PAS protocol with a new PAS protocol to fulfill the post-approval requirement. The new PAS protocol supersedes the previous protocol.
Terminated	The sponsor has not fulfilled or cannot fulfill the post-approval requirement identified in the condition(s) of approval (PAS requirement), e.g., postmarket questions are no longer relevant, device is not currently being sold and sponsor withdraws premarket submission that received the PAS as condition of approval. If FDA determines that all appropriate efforts to fulfill the condition of approval have been exhausted, FDA intends to terminate the study.
Hold	This status reflects when a study has been placed on a hold temporarily. Examples of situations when a PAS might be temporarily paused include the following examples: • while a change in ownership is completed, a pending separate study is being used to address condition of approval, or

- ceased device sales, but the premarket submission associated with the PAS is not withdrawn.

When the circumstances necessitating the hold have resolved, the sponsor is responsible for resuming the PAS. The progress is assessed against approved study milestones.

XI. Failure to Complete a Post-Approval Study

There may be circumstances that make it impossible or inappropriate for the sponsor to complete a PAS. For instance, the sponsor may have instituted a voluntary withdrawal or recall of the device from the market that impacts the sponsor's ability to complete the PAS. The sponsor should communicate any such circumstances to FDA as soon as possible.

In addition, if FDA believes the PAS cannot be completed as designed or because of data inadequacies, FDA intends to discuss with the sponsor the need to redesign the PAS and, establish a new PAS protocol and timelines to fulfill the PAS requirement. We recommend that the sponsor initiate early communication with FDA if they encounter barriers that limit their ability to fulfill your PAS requirement.

If FDA concludes the sponsor has not complied with a PAS requirement and the sponsor has not provided a valid 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 FD&C Act. In appropriate instances, FDA may order postmarket surveillance under section 522 of the FD&C Act. Note that the failure or refusal to comply with section 522 is a prohibited act under section 301(q)(1)(C) of the FD&C Act, 21 U.S.C. 331(q)(1)(C). Further, under section 502(t)(3) of the FD&C 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 FD&C 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.

XII. Public Disclosure of Post-Approval Study Information

A. Website

To increase transparency to FDA stakeholders, including consumers, patients, physicians, and industry, FDA posts certain information about PAS (e.g. study description and interim or final study results, see details below) on the webpage for the PAS Program Database.[24] This information will be posted in compliance with the requirements of 21 CFR 814.9 on the confidentiality of data and information in the PMA file and 21 CFR Part 20 on the public disclosure of information.

PAS-related information that may be posted includes:

[24] https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/PMA_pas.cfm.

General Information

- PMA number
- sponsor name
- device name
- medical specialty (e.g., cardiovascular, orthopedic)
- date of issuance of PMA approval order
- PAS name
- PAS protocol approval date
- PAS status

General PAS Parameters

- study design
- data source(s)
- comparison group, if applicable
- analysis type (i.e., descriptive, analytic)
- study population

Detailed PAS Parameters

- detailed description of the study design
- study milestones (in the PMA approval order)
- required sample size (number of subjects and sites)
- detailed description of study population
- detailed description of data collection
- follow-up visits and length of follow-up (when applicable)

Interim PAS Report Data

FDA intends to post on its website or otherwise make public PAS interim summary data and/or FDA analyses thereof when appropriate to protect the public health, for example, when interim results raise safety concerns or may otherwise impact treatment. FDA generally considers such data to be publicly releasable in accordance with applicable disclosure laws, such as the Freedom of Information Act. Examples of interim report data that FDA may publicly disclose includes:

- number of subjects enrolled
- number of sites enrolled
- interim safety/effectiveness findings, as identified in the approved PAS study protocol.

Final PAS Report Results (where applicable)

FDA intends to post on its website or otherwise make public PAS final summary data and/or FDA analyses when studies are completed. FDA generally considers such data to be publicly releasable in accordance with applicable disclosure laws, such as the Freedom of Information Act.

Final PAS data that is posted include:

- final number of study subjects enrolled
- final number of study sites enrolled
- subject follow-up rate
- final safety/effectiveness findings and results
- FDA's interpretation and summation of the study strengths/weaknesses and if a labeling update is recommended.

Reporting Information

- PAS Progress Report and Final PAS Report schedule
- due date(s) for interim and final reports (based on schedule in the PMA approval order)
- FDA receipt date(s) of PAS Progress Report and Final PAS Report
- receipt status category for PAS Progress Report and Final PAS Report

B. Advisory Panels

FDA may seek the advice of an Advisory Panel when considering the initiation or progress of a PAS. These Advisory Panels are composed of experts outside FDA who independently review information and make recommendations to FDA.[25] Although not always part of an Advisory Panel meeting, in order to, for example, help ensure the Advisory Panel is kept current on the progress of a certain PAS, FDA may present or request that the sponsor present the status or outcomes of a PAS during a scheduled public meeting. When asked to present at such meetings, we recommend that the sponsor's presentation contains the report contents described in Section VI. FDA's presentations at such meetings are anticipated to include our analysis and evaluation of the PAS.

[25] *See* FDA Guidance "Preparation and Public Availability of Information Given to Advisory Committee Members", issued August 1, 2008, available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/preparation-and-public-availability-information-given-advisory-committee-members. *See* also FDA Guidance "Procedures for Meetings of the Medical Devices Advisory Committee," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/procedures-meetings-medical-devices-advisory-committee. *See* also the "Medical Devices Advisory Committee Charter," available at https://www.fda.gov/advisory-committees/medical-devices-advisory-committee/charter-medical-devices-advisory-committee.