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

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Guidance for Industry and Food and Drug Administration Staff

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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.

This guidance supersedes "Procedures for Handling Post-Approval Studies Imposed by PMA Order," issued on June 15, 2009.

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

Preface

Public Comment

You may submit electronic comments and suggestions at any time for Agency consideration to https://www.regulations.gov. Submit written comments to the Dockets Management Staff, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD 20852. Identify all comments with the docket number FDA-2005-D-0027. 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. 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

Guidance for Industry and Food and Drug Administration Staff

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff or Office responsible for this guidance as listed on the title page.

I. Introduction

Evaluation of premarket approval applications (PMA) by 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 circumstances when FDA has uncertainty regarding certain benefits or risks of the device, but the degree of uncertainty is acceptable in the context of

[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.

the overall benefit-risk profile of the device at the time of premarket approval.[4]

The purpose of this guidance document 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;
- 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.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

II. Background

FDA established an internal tracking system for the PAS Program in 2006, and since that time, has implemented initiatives to increase transparency, including the establishment of the webpage for the Post-Approval Studies Program Database.[5] 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, FDA may provide updates on the status of certain PAS requirements during public meetings of a Medical Device Advisory Committee Panel (an "Advisory Panel") and, in the past, has invited sponsors to provide PAS updates to help ensure Advisory Panels are kept current on

[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.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma_pas.cfm.

the progress of a certain PAS. FDA may also provide PAS updates through other public communications.

These PAS program initiatives aim to help ensure that:

- sponsors conduct PAS that use valid scientific methodologies in the study design;
- least burdensome[6] approaches, including use of relevant and reliable real-world data (RWD),[7] are followed when designing and conducting a PAS, as appropriate;
- 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).[8] 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; 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 collaboratively 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 and the importance of timely postmarket data collection for ensuring continued device safety and effectiveness, the enrollment milestones below are recommended in developing your study protocol for clinical studies.

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[6] *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.

[7] *See* FDA Guidance, "Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-real-world-evidencesupport-regulatory-decision-making-medical-devices.

[8] *See* 21 CFR 814.82(a)(2).

- First subject enrolled within 6 months of the study protocol approval date[9]
- 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

These recommended milestones are intended to be reflective of those that are most likely to result in successful PAS completion in a timely manner. FDA expects for manufactures to meet PAS requirements outlined in the PMA approval order and FDA intends to use the milestones identified in the approval order to assess study status.

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

IV. Post-Approval Study Protocols

In general, when a PAS is required as a condition of approval of the PMA, prior approval of the PAS protocol[10] is included as part of the condition. Sponsors should engage with FDA as early as possible in the PMA review to discuss the need for and details of a PAS protocol. FDA intends to review the PAS protocol interactively with the sponsor during the review of the PMA. Section IV.B. and Section IV.C. describe the process for submission and review of PAS protocols and changes after PMA approval.

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, source of comparator group, and targets for ensuring diversity with respect to sex,[11] age, race, and ethnicity[12], as appropriate)
- enrollment and recruitment plan
- sample size calculation that is statistically justified and based on study hypothesis, where

[9] The date of the PAS protocol approval is the date the PMA or PMA supplement, which includes the full PAS protocol, is approved.
[10] Use of the term "protocol(s)" throughout this guidance is intended to reflect the complete study plan which includes PAS protocol, data collection forms, informed consent forms, IRB documentation, and enrollment milestones/study timelines.
[11] *See* FDA guidance, "Evaluation of Sex-Specific Data in Medical Device Clinical Studies" (available at https://www.fda.gov/media/82005/download).
[12] *See* FDA guidance, "Evaluation and Reporting of Age-, Race-, and Ethnicity-Specific Data in Medical Device Clinical Studies" (available at https://www.fda.gov/media/98686/download).

applicable
- primary and secondary endpoints, when applicable, including definitions for study endpoints and list of adverse events/complications
- 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 estimated follow-up rates
- 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)
- interim data release plan (include frequency of interim analyses, type of analysis, data endpoints that will be assessed, content (i.e., endpoints to be posted) and proposed frequency of posting on the FDA's PAS Program Database webpage), when appropriate
- data collection forms
- informed consent forms
- Institutional Review Board (IRB) approval documentation
- enrollment milestones and study timelines (see Section III)

B. Post-Approval Study Protocol Review

When a PAS is likely to be required as a condition of approval of the PMA, 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, frequency of assessments, and enrollment milestones), 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

[13] *See* FDA guidance "Patient Engagement in the Design and Conduct of Medical Device Clinical Investigations: Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders" (available at: 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.

PMA supplement[14] within 30 calendar days[15] of the PMA approval date.[16] 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[17]. 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 the PMA approval date.

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

If you wish to propose a change to an approved PAS protocol (e.g., changes to sample size, endpoints, follow-up assessments) or to data collection forms, informed consent forms, and IRB documentation 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.

FDA understands that study delays sometimes may occur, however, FDA generally does not intend for sponsors to routinely modify the PAS protocols in order to adjust study milestones. Sponsors may request changes to the original enrollment milestones identified in the PMA approval order and FDA intends to consider these on a case-by-case basis.[18] An example of where a change to the original study milestone could be appropriate might be when new information indicates that the original study enrollment milestones were impractical at the time of the PMA approval order. Based on past experience, FDA expects that it may be appropriate in limited circumstances to revise the original study milestones in the PMA approval order and intends to determine the study progress and to designate its status (e.g., as pending, ongoing, or delayed) based on the milestones specified in the PMA approval order. See Section V and Section VI.C. for recommendations regarding the communication of anticipated or occurring study delays in progress reports. See Section VII for considerations for mitigating study delays.

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

[14] PMA supplements containing only a PAS protocol should be submitted as supplements with no user-fee. *See* FDA's guidance "User Fees and Refunds for Premarket Approval Applications and Device Biologics License Applications" (available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/user-fees-and-refunds-premarket-approval-applications-and-device-biologics-license-applications)

[15] Use of the term "calendar days" throughout this guidance is intended to distinguish calendar days from working days.

[16] *See* 21 CFR 814.82(a).

[17] FDA intends to review study protocols within 60 calendar days of PMA approval but actual review times may be longer in certain cases, such as when there is a government shutdown or other disruptions to normal operations.

[18] Proposed changes to study enrollment milestones should be submitted as a PMA supplement. Such requests should not be combined with any other requests for changes to the PAS protocol.

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 webpage[19] (see Section X for more information on study status).

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

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.[20] 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, and safety and effectiveness data (see Section VI for additional report content details). When delays are anticipated or are occurring, sponsors should notify FDA in the next scheduled PAS Progress Report of the delays, reasons, and plans to address challenges and meet established milestones identified in the PMA approval order. A Final PAS Report is a written report of a completed or terminated PAS.

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 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 a 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.[21] 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; 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 year of the study and annually, thereafter, from the date of the PMA approval letter or other negotiated starting date, unless a different reporting schedule is agreed upon. 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), unless a different

[19] https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma_pas.cfm.
[20] *See* 21 CFR 814.82(a)(2)
[21] FDA recommends the sponsor contact FDA if they wish to combine reports or submit one report for more than one PAS.

reporting schedule post study completion is agreed upon.

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.[22] 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. For some studies (e.g., retrospective analysis of RWD,[23] non-clinical studies), sponsors are encouraged to work with FDA to determine the applicability of the PAS Enrollment Status Report and content of any PAS reports.

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

[22] *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.

[23] *See* FDA guidance, "Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-real-world-evidence-support-regulatory-decision-making-medical-devices.

  - 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):[24]
  - 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[25]
  - Other (specify)
- Type of submission:
  - Enrollment Status Report
  - 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

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

[25] 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.

completed.[26] 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 (as applicable):

- Begin and end dates of period covered by the report
- Start and completion dates 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, including sex,[27] age, race, and ethnicity[28], as appropriate)
- Comparison of target versus actual enrollment dates based on enrollment milestones specified in the PMA approval order

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), and targets for ensuring diversity with respect to sex,[29] age, race, and ethnicity[30], as appropriate
  - total number of subjects to be enrolled
  - 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 submission of report)
- Subject accountability (e.g., enrolled, randomized, completed, withdrawn, lost to follow-up) at each follow-up timepoint, for the entire population and broken down by subgroups, if applicable. 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:
  - delays in enrollment and plans to address challenges and meet established milestones specified in the PMA approval order
  - subjects lost to follow-up, if known, as well as any measure to minimize such future

[26] For non-clinical PAS data, accrual milestone reports may be used to track progress.
[27] *See* FDA guidance, "Evaluation of Sex-Specific Data in Medical Device Clinical Studies" (available at https://www.fda.gov/media/82005/download).
[28] *See* FDA guidance, "Evaluation and Reporting of Age-, Race-, and Ethnicity-Specific Data in Medical Device Clinical Studies" (available at https://www.fda.gov/media/98686/download).
[29] *See* FDA guidance, "Evaluation of Sex-Specific Data in Medical Device Clinical Studies" (available at https://www.fda.gov/media/82005/download).
[30] *See* FDA guidance, "Evaluation and Reporting of Age-, Race-, and Ethnicity-Specific Data in Medical Device Clinical Studies" (available at https://www.fda.gov/media/98686/download).

events
  - subject and healthcare provider-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
- Proposed interim summary data to be posted on FDA's PAS Program Database webpage [31]

D. Final Post-Approval Study Status Reports

FDA recommends a Final PAS Report include (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), and targets for ensuring diversity with respect to sex,[32] age, race, and ethnicity[33], as appropriate
  - 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
- Final accountability of enrolled subjects compared to target
- Final accountability of number of subjects (e.g., enrolled, randomized, completed, withdrawn, lost to follow-up) at each study follow-up timepoint, for the entire population and broken down by subgroups, if applicable
- An explanation for:
  - subjects lost to follow-up, if known
  - subject and healthcare provider-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 remained in the study? Is the loss to follow-up differential by study group?) and potential impact on interpretation of results
- Summary and interpretation of final safety/effectiveness findings
- Proposed summary data to be posted on FDA's Post-Approval Studies (PAS) Database webpage[34]

VII. Evaluation of Interim Post-Approval Study Reports

Enrollment Status Report: FDA intends to review Enrollment Status Reports to assess progress

[31] FDA will make the final determination of what information is posted on the PAS Program Database webpage based on the totality of our review and consistent with applicable disclosure laws.
[32] *See* FDA guidance, "Evaluation of Sex-Specific Data in Medical Device Clinical Studies" (available at https://www.fda.gov/media/82005/download).
[33] *See* FDA guidance, "Evaluation and Reporting of Age-, Race-, and Ethnicity-Specific Data in Medical Device Clinical Studies" (available at https://www.fda.gov/media/98686/download).
[34] https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma_pas.cfm

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);
- protocol adherence and reasons for deviations from the methodology;
- the performance and postmarket safety and effectiveness of the device;
- whether study enrollment milestones are met (see Section X);
- causes for delays in PAS progress or failure to meet enrollment milestones and plan to address challenges and meet established milestones;
    - When a sponsor fails to meet enrollment milestone requirements, FDA expects sponsors to act with due diligence to mitigate continued study delays. FDA intends to consider the sponsors' mitigation efforts to address study delays. Mitigation efforts may include, but are not limited to, the following:
        - current and past enrollment recovery efforts;
        - evaluation of slow enrollment;
        - device availability on the market;
        - measures taken to initiate study sites;
        - measures taken to incentivize study subjects;
        - outreach to study investigators and potential subjects; and
        - plans to remove barriers to site and subject participation.

Although it is recommended that the sponsor identify any missed milestones as part of PAS reports, the sponsor should communicate circumstances which are impacting their ability to meet PAS requirements to FDA as soon as possible.

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 the sponsor failed to meet enrollment milestones or study timelines, FDA ultimately may take enforcement actions to ensure compliance with PAS requirements, as appropriate (see Section XI). Additionally, if the PAS results identify new safety and/or effectiveness concerns for a device, FDA may consider taking actions, which may include issuing a Safety Communication to provide recommendations on patient management, 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 interactively and/or through a deficiency letter. Additionally, if the PAS results identify new safety and/or effectiveness concerns for a device, FDA may consider taking action, which may include issuing a Safety Communication, as appropriate.

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).[35]

IX. Sponsor's Reporting Status

Upon receipt of a 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[36] for each PAS Progress and Final Report submission. The reporting status categories are described in Table 1 below.

[35] PMA supplements that include only labeling changes reflecting the results from a PAS should be submitted as supplements with no user-fee. *See* FDA's guidance "User Fees and Refunds for Premarket Approval Applications and Device Biologics License Applications" (available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/user-fees-and-refunds-premarket-approval-applications-and-device-biologics-license-applications)

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

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 a 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.[37] 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. 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 (see Section IV.C.). Each of these status categories are described in Table 2 below.

Table 2. PAS Status Category

Status	Definition
Protocol Pending	This category is used when a protocol was not approved at the time of the PMA approval order 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.

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

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 report.
Ongoing	The study is proceeding according to, or is ahead of, the study timelines specified in the PMA approval order. 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 PAS protocol**.**
Delayed	The progression of the study is behind the study timelines specified in the PMA approval order. 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 enrollment milestones specified in the PMA approval order 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 Requirement

There may be circumstances that make it impossible or inappropriate for the sponsor to complete a PAS requirement. 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.

In addition, if FDA believes the PAS cannot be completed as designed or can no longer address the study questions, 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 the ability to fulfill their 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 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 misbranding under section 502(t)(3) may lead to enforcement actions including seizure, injunction, prosecution, or civil money penalties.

XII. Public Disclosure of Post-Approval Study Information

A. FDA Website

To increase transparency to FDA stakeholders, including consumers, patients, healthcare providers, 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.[38] 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:

General Information

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

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

- 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)
- description of study population
- description of study endpoint(s)
- 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 results consistent with the interim data release plan (included as part of the PAS protocol) and may post additional information that may be beneficial for public awareness. If the PAS protocol does not include an interim data release plan, FDA intends to post PAS interim summary data and/or FDA analyses thereof when appropriate to protect the public health, such as in cases where interim results raise safety concerns, serve to provide critical device performance information, 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. When sharing information appropriate to protect public health, FDA will consider the benefits of sharing the information, as well as other considerations on the study conduct. Examples of interim report data that FDA may publicly disclose includes:

- number of subjects enrolled
- number of sites enrolled
- interim safety/effectiveness findings.

However, if a sponsor believes in a particular instance that interim results are restricted from public release; for example, because they constitute personal identifying information, trade secrets, or confidential commercial information, they should notify FDA of this in the interim report containing the results and explain why they believe disclosure of the data is restricted.

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 may 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, or for input on data that raise concerns regarding the safety and/or effectiveness of a device. These Advisory Panels are composed of experts outside FDA who independently review information and make recommendations to FDA.[39] 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.

[39] *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.