Welcome To Today's Webinar

Thanks for joining us!

We'll get started in a few minutes

Today's Topic:

Postmarket Mandated Studies Programs: Overview and Final Guidance Updates

December 6, 2022

Postmarket Mandated Studies Programs: Overview and Final Guidance Updates

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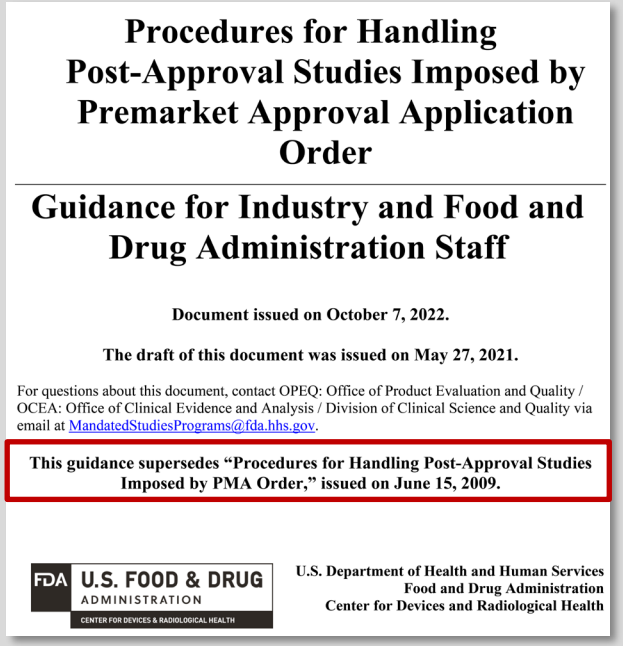
Final Guidance Documents



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

Guidance for Industry and Food and Drug Administration Staff

Document issued on October 7, 2022.

The draft of this document was issued on May 27, 2021.

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.

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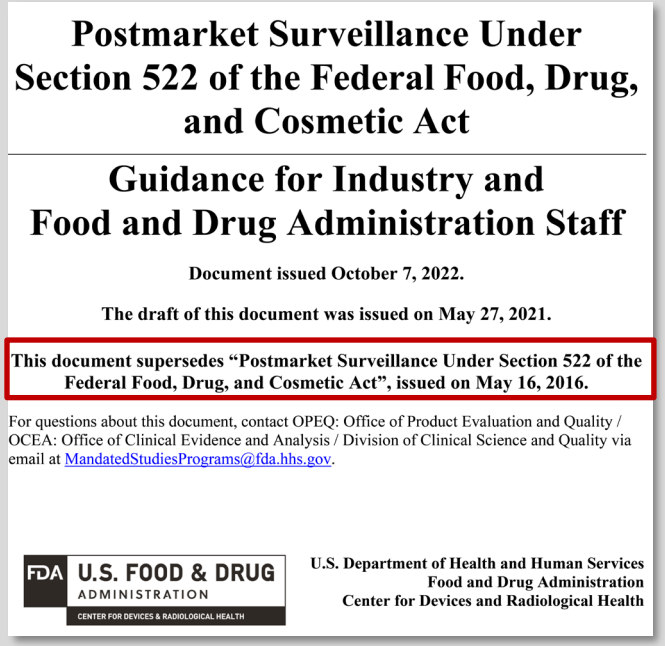
www.fda.gov/regulatory-information/search-fda-guidance-documents/procedures-handling-post-approval-studies-imposed-pma-order



Postmarket Surveillance Under Section 522 of the Federal Food, Drug, and Cosmetic Act

Guidance for Industry and Food and Drug Administration Staff

Document issued October 7, 2022.

The draft of this document was issued on May 27, 2021.

This document supersedes "Postmarket Surveillance Under Section 522 of the Federal Food, Drug, and Cosmetic Act", issued on May 16, 2016.

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.

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www.fda.gov/regulatory-information/search-fda-guidance-documents/postmarket-surveillance-under-section-522-federal-food-drug-and-cosmetic-act

Learning Objectives

- Provide background information on the Postmarket Mandated Studies Programs
- Discuss major stakeholder comments on the draft Post-Approval Studies (PAS) and Postmarket Surveillance (522 studies) guidance documents
- Outline the purpose and scope of the PAS and 522 studies final guidance documents
- Identify updates included in the PAS and 522 studies final guidance documents

BACKGROUND

Medical Device Safety

*"[*Our goal for safety is*] …ensuring that the FDA is consistently first among the world's regulatory agencies to identify and act upon safety signals related to medical devices…"*

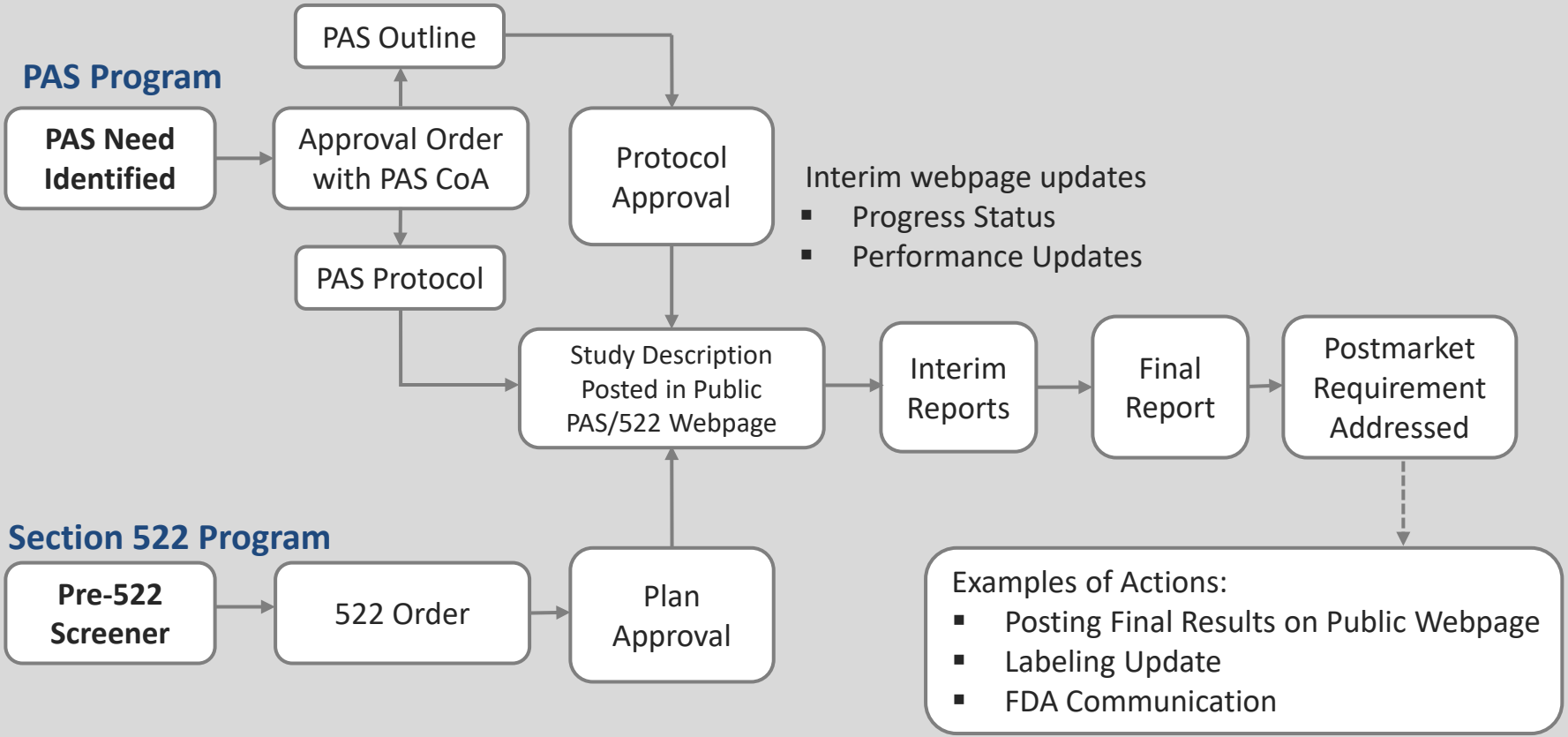
Statement from FDA Commissioner Scott Gottlieb, M.D. and Jeff Shuren, M.D., November 2018

Overall Goal

- Recommendations on the format, content, and review of PAS and 522 submissions
- Clear sponsor expectations for study timelines
- Timely FDA review of postmarket information

Guidance Timeline

Postmarket Mandated Studies Programs Overview



STAKEHOLDER COMMENTS ON DRAFT GUIDANCES DOCUMENTS

Stakeholder Comments

Timelines

- Enrollment milestones are too prescriptive and depend on the study design
  - These are recommended enrollment milestones based on FDA's experience with mandated studies
- The timeline for sponsor submission of protocols/plans and final reports is insufficient
  - The recommended timeline to submit final reports is consistent with previous guidance document(s)

Stakeholder Comments

Transparency

- Web posting of interim results could result in release of confidential information and misinterpretation of results
  - FDA generally considers the information to be posted on the website 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
- Sponsors requested an opportunity to review information before it is posted
  - Sponsors will have the opportunity to propose summary data for the website in reports

PURPOSE AND SCOPE

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

www.fda.gov/regulatory-information/search-fda-guidance-documents/procedures-handling-post-approval-studies-imposed-pma-order

PAS Regulatory Authority

- Class III devices
- Section 513(a)(3)(C) of the FD&C Act
  - FDA may consider whether postmarket data collection or other conditions might be structured to permit approval subject to those conditions
- 21 CFR 814.82(a)(2) for PMAs
  - Post-Approval studies can be imposed at time of approval to continue evaluation and reporting on the safety, effectiveness, and reliability of the device for its intended use

PAS Rationale

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

*See FDA guidance documents entitled "*Balancing Premarket and Postmarket Data Collection for Devices Subject to Premarket Approval" *and* "Consideration of Uncertainty in Making Benefit-Risk Determinations in Medical Device Premarket Approvals, De Novo Classifications, and Humanitarian Device Exemptions."

PAS Guidance Structure

I. Introduction
II. Background
III. PAS Requirements in PMA Approval Order
IV. PAS Protocols
V. When and How to Submit PAS Reports
VI. Content and Format of Interim and Final PAS Reports
VII. Evaluation of Interim PAS Reports
VIII. Evaluation of Final PAS Reports
IX. Sponsor's Reporting Status
X. Study Status
XI. Failure to Complete a PAS Requirement
XII. Public Disclosure of PAS Information

Postmarket Surveillance Under Section 522 of the Federal Food, Drug, and Cosmetic Act

www.fda.gov/regulatory-information/search-fda-guidance-documents/postmarket-surveillance-under-section-522-federal-food-drug-and-cosmetic-act

522 Regulatory Authority

- Class II and III devices
- Section 522 of the FD&C Act
  - [FDA] may, by order, at the time of approval or clearance of a device or at any time thereafter, require a manufacturer to conduct postmarket surveillance… for a prospective surveillance of up to 36 months*
  - Surveillance must commence within 15 months of the order
- 21 CFR 822 Postmarket Surveillance
  - "The purpose of this part is to implement our postmarket surveillance authority to maximize the likelihood that postmarket surveillance plans will result in the collection of useful data. These data can reveal unforeseen adverse events, the actual rate of anticipated adverse events, or other information necessary to protect the public health." (*See 21 CFR 822.2*)

*Can be longer for devices with expected significant use in pediatrics

522 Statutory Criteria

Section 522 of the FD&C Act permits FDA to require postmarket surveillance for class II or III devices that meet any of the statutory criteria:

Section 522 of the FD&C Act Criteria	
Criterion 1	Failure of the device would be reasonably likely to have a **serious adverse health consequence**.
Criterion 2	*Expected* to have **significant use** in pediatric populations.
Criterion 3	Intended to be **implanted in the body for more than one year**.
Criterion 4	Intended to be a **life-sustaining or life-supporting device used outside of a device user facility**.

522 Guidance Structure

I. Introduction
II. Pre-522 Postmarket Surveillance Process
III. Postmarket Surveillance Plans
IV. When and How to Submit Postmarket Surveillance Reports
V. Content and Format of Postmarket Surveillance Reports
VI. Evaluation of Interim Postmarket Surveillance Reports
VII. Evaluation of Postmarket Surveillance Final Reports and Possible FDA Actions After 522 Order Completion
VIII. Manufacturer's Reporting Status
IX. Postmarket Surveillance Status
X. Failure to Comply with Postmarket Surveillance Requirements under Section 522 of the FD&C Act
XI. Public Disclosure of Postmarket Surveillance Plan Information and Reports

Appendix 1: Section 522 Administrative Checklist Review

GUIDANCE UPDATES

PAS/522 Guidance Updates

A. Timely submission and review of PAS protocols/522 plans and reports

B. Recommendations on study timeline/enrollment milestones

C. Submission of changes to an approved PAS protocol/522 plan

D. Study status categories

E. Transparency of posting interim/final results

F. Content of PAS protocols/522 plans and reports

- Minor updates to recommended elements

A. Timely Submission and Review of PAS Protocols/522 Plans

- Sponsors and FDA should work collaboratively
  - Early interactions (when possible)
- FDA intends to review PAS protocols/522 plans and issue a decision within 60 days of the approval/522 orders

Submission Type	Sponsor Submission Timeline	FDA Review Goal
PAS Protocol	Submit with PMA or w/in 30 days* of order if PAS protocol not approved with PMA	Within 30 days of receipt
522 Plan	Submit within 30 days of order‡	Within 30 days of receipt§

* per approval orders

‡ section 522(b)(1) of the FD&C Act and 21 CFR 822.8

§ per 21 CFR 822.17, FDA will review the 522 plan and respond within 60 days of receipt

Timely Submission and Review of Reports

Report Type*	Studies with New Enrollment	Studies without New Enrollment
Progress	Semiannual until 100% enrolled†, annually thereafter	Semiannual in 1st year, annually thereafter
Enrollment	As specified in the approval order or approved 522 plan	
Final	Three months from study completion (i.e., last subject's last follow-up date)	

* FDA intends to review interim reports and final reports within 30 days and 60 days of receipt, respectively.
† For the first 2 years and annually thereafter for 522 studies.

NOTE: Reporting schedule will be included in the PMA approval order or approved 522 plan
PAS Reporting from the date of the PMA approval order (or other agreed-upon starting date)
522 Reporting from the date of the 522 plan approval (or other agreed-upon starting date)

B. Study Timelines/ Enrollment Milestones

- Recommendations to ensure timely initiation and completion of PAS/522 studies

Subject Enrollment	PAS Timeline*	522 Timeline†
1st Subject	6 months	15 months‡
20%	12 months	18 months
50%	18 months	21 months
100%	24 months	24 months

* From study protocol approval date
† From date of issuance of the 522 order
‡ Per section 522(b)(1) of the FD&C Act

C. Changes to Approved PAS Protocol/522 Plan

- FDA generally does not intend for sponsors to routinely modify the PAS protocols/522 plans
  - FDA will consider changes on a case-by-case basis
  - Example of an appropriate change: When new information indicates that the original study enrollment milestones were impractical at the time of the PMA approval order/approval of 522 plan

- FDA expects, only in limited circumstances, revisions to the original study milestones in the PMA approval order/approved 522 plan

- FDA will determine the study progress and designate study status based on the milestones specified in the PMA approval order/approved 522 plan

Reporting Study Delays and Mitigation Plans

- Reports should include:
  - the causes for delays in study progress or failure to meet enrollment milestones; and
  - a plan to address challenges and meet established milestones.
- Mitigation efforts may include:
  - 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.

D. Updated Study Status Categories

Previous Study Status Category	Updated Study Status Category
Progress Adequate	**Ongoing:** Study proceeding according to, or is ahead of, the study timelines in the approval order or the 522 plan.
Progress Inadequate	**Delayed:** Study behind the study timelines in the approval order or 522 plan.
Revised/Replaced*	**Redesigned/Replaced:** Study requirement cannot be fulfilled as originally designed and FDA has agreed to redesign or replace the PAS protocol/ 522 plan to fulfill the requirement.
Other	**Hold:** Study has been placed on a hold temporarily, for example, because the device is no longer sold but the premarket submission associated with the requirement has not been withdrawn.

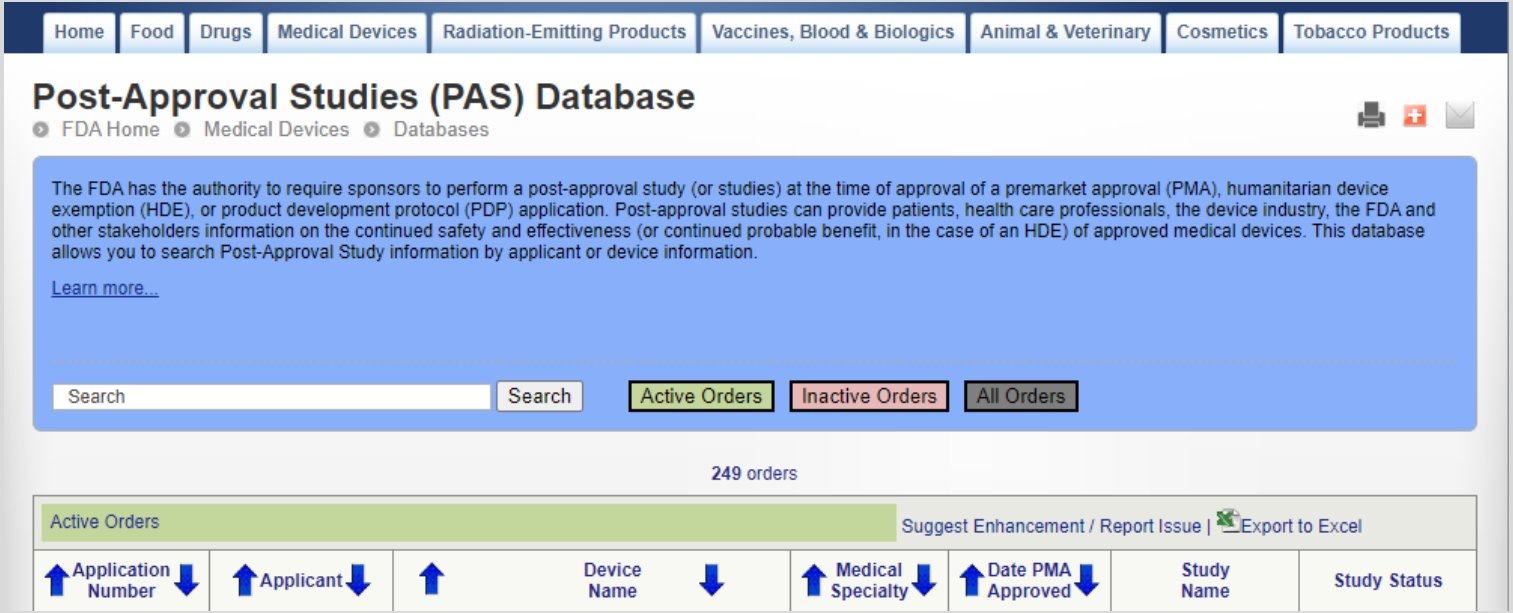
*Revised/Replaced was previously only included in the 522 Guidance.

Updated Study Status Categories

- New study status categories apply to new submissions received after publication of the final guidance documents (**October 7, 2022**)
- For any submission received prior to **October 7, 2022**, the former study status categories will be used
- During a transition period, the Programs webpages will include both former and current study status categories until all study requirements receive a submission and FDA issues a decision on that submission

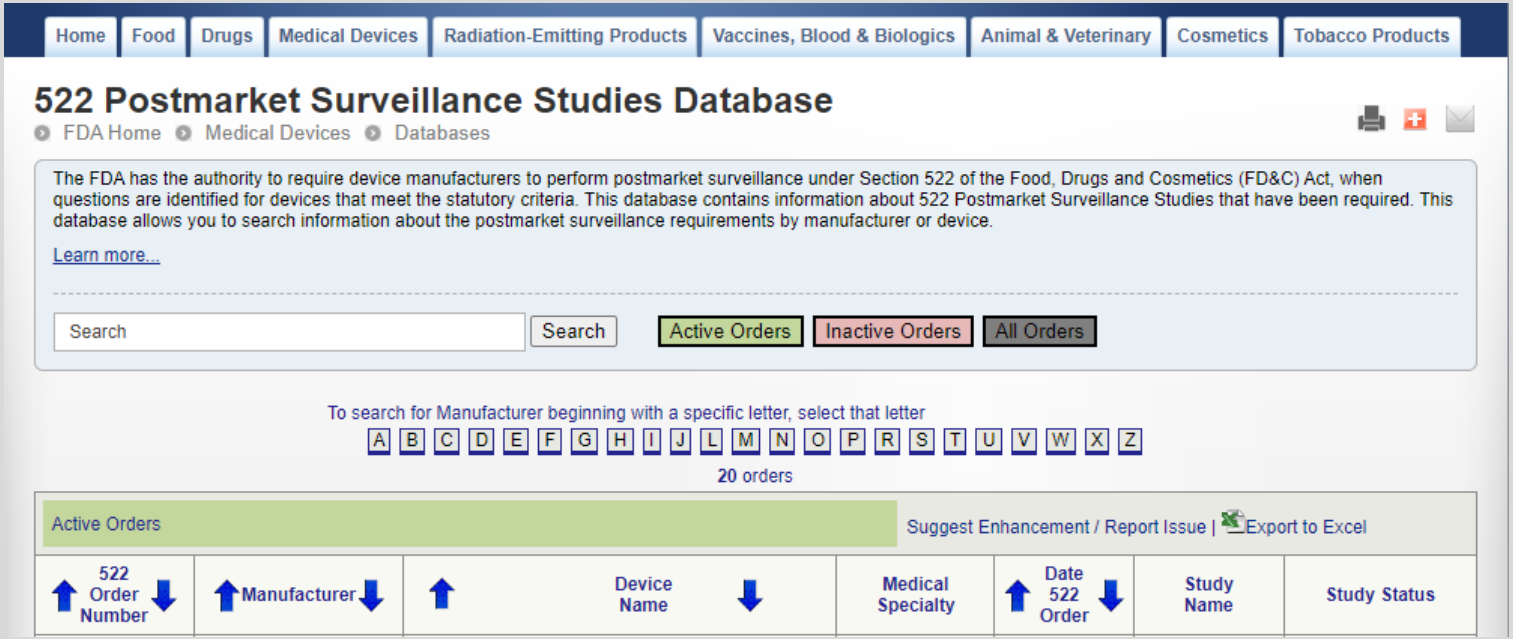
E. PAS Database

www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_pas.cfm



E. 522 Studies Database

www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pss.cfm



E. PAS/522 Transparency

- FDA intends to post on its website, or otherwise make public, study interim results consistent with the Interim Data Release Plan
  - Consistent with the Interim Data Release Plan; and/or
  - When appropriate to protect public health
- Interim Data Release Plan in the PAS protocol/522 plan
  - Frequency and type of interim analyses, data endpoints to be assessed and posted, and proposed frequency of posting on the FDA's websites
- Sponsors can propose summary data in progress and final reports

Additional Resources

- Program Webpages
  - Post-Approval Studies Program: www.fda.gov/medical-devices/postmarket-requirements-devices/post-approval-studies-program
  - 522 Postmarket Surveillance Studies Program: www.fda.gov/medical-devices/postmarket-requirements-devices/522-postmarket-surveillance-studies-program

- Mandated Studies Programs Email
  - MandatedStudiesPrograms@fda.hhs.gov

Summary

- Postmarket mandated studies are important tools to ensure continued device safety and effectiveness
- Guidance document updates focused on activities to address postmarket questions in a timely manner
  - Early and ongoing communication with manufacturers
  - Collaborative establishment of protocol/plan, enrollment milestones, and study completion timelines to ensure that the studies achieve objectives and are completed in a timely manner
  - Timely reporting, review, and public posting of postmarket study information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Let's Take Your Questions

- **To Ask a Question:**
  1. Raise your hand in Zoom 

  2. Moderator will announce your name and invite you to ask your question
  3. Unmute yourself when prompted in Zoom to ask your question

- **When Asking a Question:**
  - Ask one question only
  - Keep question short
  - No questions about specific submissions

- **After Question is Answered:**
  - Mute yourself and lower your hand
  - If you have more questions - raise your hand again

Thanks for Joining Today!

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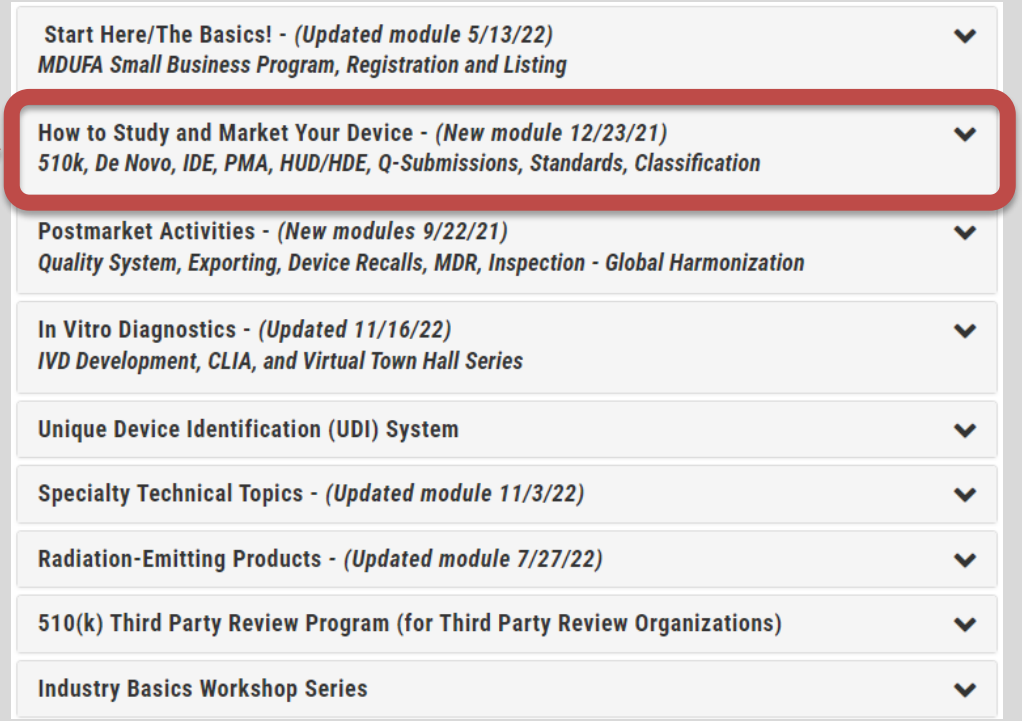


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