**Post-Approval Study Requirements and Postmarket Surveillance under Section 522 of the Federal Food, Drug, and Cosmetic Act, Final Guidances**

**(Postmarket Mandated Studies Programs: Overview and Final Guidance Updates)**
**December 6, 2022**

**Moderator: CDR Kim Piermatteo**

**CDR Kim Piermatteo:** Hello, and welcome to today's CDRH webinar. Thank you for joining us today. This is Commander Kim Piermatteo of the United States Public Health Service and I serve as the Education Program Administrator in the Division of Industry and Consumer Education in CDRH's Office of Communication and Education. I'll be your moderator for today's webinar.

Our topics today are the two final guidances titled "Procedures For Handling Post-Approval Studies Imposed by Premarket Approval Application Order" and "Postmarket Surveillance Under Section 522 of the Federal Food, Drug, and Cosmetic Act," which were both issued on October 7th, 2022.

These guidances are intended to enhance patient safety by facilitating timely initiation and completion of post-approval studies and postmarket surveillance under Section 522 of the Federal Food, Drug, and Cosmetic Act. These guidances are also intended to increase transparency on the FDA's approach to the issuance and tracking of post-approval study requirements and 522 orders. We are holding this webinar to provide you with an opportunity to learn more and to answer any questions you may have about these final guidances.

It's my pleasure now to introduce you to our presenter for today's webinar, Dr. Erika Tang, Epidemiologist in the Division of Clinical Evidence and Analysis 1, specifically Clinical Policy and Quality, and the Office of Clinical Evidence and Analysis, or OCEA, within CDRH's Office of Product Evaluation and Quality, or OPEQ.

We'll begin with a presentation from Erika, and then field your questions about these topics. As a friendly reminder, for those of you participating live in today's CDRH webinar, please be sure you have joined us via the Zoom app and not through a web browser to avoid any technical issues.

Thank you all again for joining us. I'd now like to turn it over to Erika to start today's presentation. Erika…

**Erika Tang:** Thank you, Kim. Good afternoon, everyone and welcome to this CDRH webinar. Today, I will present an overview of the post-market mandated studies programs and describe the updates included in the recently published final guidance documents.

We are very excited with the recent publication of the final guidance documents on "Procedures for Handling Post-Approval Studies Imposed by Premarket Approval Application Orders" and "Postmarket Surveillance Under Section 522 of the Federal Food, Drug, and Cosmetic Act," which I will be referring as 522 studies. These are updates to guidance documents that have been in use since 2009 for post-approval studies and since 2016 for 522 studies. These updated guidances supersede the prior guidance documents.

Our learning objectives for today's webinar are listed here. By the end of the webinar, we hope that participants will be able to provide background information on the Postmarket Mandated Studies Programs, which is a term to collectively refer to the programs for post-approval studies and 522 studies. Discuss major stakeholder comments on the draft PAS and 522 studies guidance documents, outline the purpose and scope of the final guidance documents, and identify updates included.

So let's begin with the background information on the postmarket mandatory studies programs.

Our motivation to update the guidance documents is to support FDA's goal for safety by ensuring that the FDA is consistently first among the world's regulatory agencies to identify and act upon safety signals related to medical devices.

Our overall goal in these efforts, including the update of the guidance documents, is to assist stakeholders with understanding PAS requirements and 522 orders by providing recommendations on the format, content, and review of PAS and 522 study submissions. Provide clear sponsor expectations for study timelines, and have timely FDA review of postmarket information.

This slide provides a general timeline of the development of the updated guidance documents. The draft were published on May 27 of last year, and commentors provided feedback to the agency through the last week of July of 2021. It was important to address these comments and incorporate them into the final guidance documents that were issued two months ago on the 7th of October.

As background, I would like to take a minute to show you a high-level overview of the PAS and the 522 programs. After identifying the need for a post-approval study, the review team works with the sponsor to establish a PAS protocol prior to device approval. For the 522 program, when FDA identifies a potential issue with a device, the review team may assess whether a 522 order is appropriate.

A device with a post-approval study as a condition of approval could be approved with a PAS protocol or on some occasions with a study outline. Within 30 days of the approval order, sponsors are required to submit the PAS protocol if the device was approved with a study outline. After a 522 order is issued, a sponsor also have 30 days to submit the 522 plan for FDA's review.

Once the protocols and plans are approved, a summary of the studies is posted on the program's public web pages. Also, after the protocols and plans are approved, the sponsors submit interim reports to FDA throughout the course of the study, and the program web pages are updated with the study progress and device performance from the interim reports.

Upon study completion, a sponsor submit a final report and the review team determines if the postmarket requirements are addressed. The review team will also assess if other actions, in addition to posting the final results on the web pages, are needed. For example, if the sponsor needs to update the label to include the study results. The guidance documents cover all of these different steps shown here.

I will present next a summary of the major comments the agency received from stakeholders. The major comments were common to both draft guidance documents and fell into two main categories, timelines and transparency.

First, I will go over the major comments we receive on timelines. Stakeholders have concerns that enrollment milestones are too prescriptive and depend on the study design. The final guidance

documents make clear that these are recommended enrollment milestones based on FDA's experience with mandated studies. We also highlighted in the guidance documents that the recommended milestones are intended to be reflected of those that are most likely to result in successful study completion in a timely manner. The guidance documents also encourage the sponsors and FDA to work together to establish a PAS protocol and 522 plan, including enrollment milestones.

The other major comment was that the timeline for sponsor submission of protocols, plans, and final reports is insufficient. To meet the submission deadlines of PAS protocols and 522 plans, the guidance documents recommend sponsors and staff to use early and ongoing interactions as the primary methods to discuss PAS protocols and 522 plans. For final reports, the recommended timeline to submit them is consistent with previous guidance documents. And based on FDA's experience, the final report timeline has been achievable for most studies.

The second category of major comments from stakeholders was on transparency. The stakeholders were concerns that web posting of interim results could result in release of confidential information and misinterpretations of results. FDA generally considers the information to be posted on its website to be publicly releasable in accordance with applicable disclosure laws such as the Freedom of Information Act.

In addition, 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. Another comment on this category was that the sponsors requested an opportunity to review information before it is posted. The recommended items included in interim and final report were updated in the final guidance documents to give an opportunity to sponsors to propose summary data for the program web pages.

In the next slides, we will go over the purpose, scope, and structure of each of the guidance documents for the mandated studies programs.

Let's start with the post-approval studies program. The purpose of the PAS guidance document is to assist stakeholders with understanding PAS requirements imposed as a condition of PMA approval.

FDA has regulatory authority to impose a post-approval study requirement as a condition of approval for Class III devices. This authority is under Section 513 of the Act, under which we may consider whether postmarket data collection or other conditions may be structured to permit approval subject to those conditions.

21 CFR 814.82 for premarket approval applications also states that post-approval studies can be imposed at the time of the approval to continue evaluation, and reporting on the safety, effectiveness, and reliability of the device for its intended use.

The rationale for a post-approval study is that FDA may consider it acceptable to collect certain data in the postmarket setting, rather than premarket, under certain circumstances when FDA has more uncertainty regarding certain benefits or risk 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. FDA's assessment of the degree of uncertainty and benefit risk profile is consistent with other guidance documents we have on those topics.

The structure of the PAS guidance document covers in the first sections the background of the PAS program, PAS requirements, and recommended elements of the PAS protocols. The following sections are focused on the content and how we evaluate interim and final reports. And the last sections cover sponsors reporting and study status, failure to complete a PAS requirement, and public disclosure of PAS information.

Now we will go over items related to the 522 studies program. The purpose of this guidance document is to assist manufacturers of devices subject to 522 orders.

FDA has the authority to require postmarket surveillance for Class II and Class III devices per the statute in section 522 of the Act, titled Postmarket Surveillance, if the device meets at least one of the criteria in the statute, which I will show you in the next slide.

FDA can issue a 522 order at the time of device approval or clearance, or at any time thereafter. Prospective surveillance is limited to up to 36 months, unless the device is suspected to have significant use in pediatrics. Surveillance must commence within 15 months of the order, which we define as when the first subject has been enrolled.

Regulations related to 522 studies are included in section 822 of the Code of Federal Regulations. 21 CFR 822 on postmarket surveillance notes that the purpose of this part is to implement a postmarket surveillance authority to maximize the likelihood that postmarket surveillance plans will result in the collection of useful data. This data can reveal unforeseen adverse events, the actual rate of anticipated adverse events, or other information necessary to protect the public health.

As I mentioned previously, section 522 of the Act permits FDA to require postmarket surveillance for Class II or Class III devices that meet any of these criteria set by section 522 of the Act. One, failure of the device will be reasonably likely to have a serious adverse health consequence. Two, the device is expected to have significant use in pediatric populations. Three, the device is intended to be implanted in the body for more than one year, or the device is intended to be a life-sustaining or life-supporting device used outside of a device user facility.

The structure of the 522 studies guidance document is similar to the structure of the PAS guidance. It covers the same general sections in the same order. But the 522 studies guidance also includes details on our internal process before a 522 order is issue.

Next, I will go over the updates to the guidance documents.

This is an overview of the updates made to the guidance documents. The updates made to both guidance documents were very similar. Therefore, I will be describing them as they apply generally to both programs for the remainder of the presentation, calling out any differences where needed. I will explain the updates to each of the items listed here in detail in the subsequent slides. Except for the last item, Item F, which is the content of PAS protocols, 522 plans, and reports. Relatively minor edits were made to the elements recommended to be included in these sections.

The first update was on timely submission and review of the PAS protocols and 522 plans. These updates help ensure that a mandated study achieves its objectives and is completed in a timely manner. FDA intends to review PAS protocols and 522 plans, initial decision within 60 days of the approval or 522 order.

The guidance documents include recommendations and requirements for submission timelines for sponsors and review timeline for FDA. Specifically, sponsors are required to submit a PAS protocol with a PMA or within 30 days of the approval order if a PAS protocol was not approved with the PMA. The sponsors are also required to submit a 522 plan within 30 days of their 522 order issue date. For both submission types, FDA intends to complete the review within 30 days of receipt.

The guidance documents present updated reporting schedules that we intend to include in the orders. For post-approval studies with new enrollment, generally we intend to require progress reports to be submitted every six months until subject enrollment has been completed and annually thereafter. For 522 studies, we intend to require progress report to be submitted every six months for the first two years and annually thereafter.

Progress report for a post-approval study without new subject enrollment-- for example, a study of the continuous follow-up of the premarket cohort-- will be required to be submitted every six months for the first year and annually thereafter. We also intend to specify in their orders the reporting schedule for enrollment status reports. For both type of mandated studies, the final report will be required to be submitted no later than three months from the study completion.

The guidance documents also provide recommendations for enrollment milestones to ensure timely initiation and completion of PAS and 522 studies. Specific recommendations are given for the enrollment of the first subject, 20%, 50%, and 100% of subjects. They were developed based on FDA's experience with mandated studies. The recommended enrollment timelines for PAS and 522 studies are very similar, but do have a slight differences, as indicated in this table. For PAS, the timelines are relative to the approval of the study protocol. And for 522 studies, the timelines are relative from the date the 522 order was issue.

The guidance documents also include recommendations on changes to approve PAS protocols or 522 plans. FDA understands that study delays sometimes may occur. However, we generally do not intend for sponsors to routinely modify the PAS protocols or 522 plans in order to adjust study milestones. FDA intends to consider this requests on a case by case basis. An example of where a change to the original study milestones 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 or approval of the 522 plan.

Based on past experience, we expect that it may be appropriate only in limited circumstances to revise the original study milestones in the PMA approval order or approved 522 plan. FDA will determine the study progress and designate the study status based on the milestones specified in the PMA approval order or approved 522 plan.

We asked the sponsors in the guidance documents to inform FDA of study delays as soon as possible, and to include in interim reports the causes for delays in study progress or failure to meet enrollment milestones in their plan to address challenges and meet established milestones. As I mentioned previously, we understand delays can happen. The guidance provides things that are important to think about as you are developing your mitigation efforts to address study delays. 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.

The guidance documents also include new study status categories. The study status categories that were changed in the updated categories are shown on this slide. The detailed definition for these categories are not included here, but generally an ongoing study is proceeding according to or ahead of the study timelines specified in the approval order or 522 plan.

Whereas a delayed study is a study behind the study timelines specified in the approval order or 522 plan. These changes were made to reflect a more objective characterization of a study progress. The revised/replaced category, a study status that was previously only included in the 522 guidance document, was changed to redesigned/replaced to better reflect this category's definition.

This category is used when a study requirement cannot fulfill as originally designed. The study status order was changed to hold, a category used when a study requirement is temporarily paused due, for example, when the sponsor has ceased device sales but the premarket submission associated with the requirement has not been withdrawn.

The updated study status categories apply to new submissions or new studies received after the publication of the guidance documents. For any file received prior to October 7, the formal study status categories will be used. This means that for an interim period, the PAS and 522 program webpages may include terms not specified in the final guidances.

The status of some studies may be marked as progress adequate, progress inadequate, other, or revised/replaced, reflecting prior policy until new information is submitted to the FDA for reviewing the study status category is changed. Next, I will show you a glimpse of each of the program's web pages.

CDRH established the post-approval studies database in the 522 postmarket surveillance studies database to share information regarding each post-approval study and each 522 study. The PAS program database provides for each post-approval study the application number, name of the applicant, device name, medical specialty, the approval date, the study name, and the study status.

In this slide, you can see that the 522 postmarket surveillance study database presents some of the same study information as the past PAS database, and also chose a specific information for the 522 studies, such as the 522 order number and the date it was issued.

In both databases, the links in the study names will take you to the study web page, which presents the detailed information on the study, such as PAS protocol or 522 study plan approval date, the study protocol or plan parameters, summary of the interim or final results, if applicable, and the sponsor's current reporting status for each submission.

In the next slide, I will go over updates made to the guidance documents to describe our approach for posting interim information, learn from the postmarket mandatory studies as they're progressing.

Information about posting interim summary data on FDA's public website was included in the previous 522 guidance document, but not in the previous PAS guidance. Both guidance documents now describe FDA's intention to post on its website interim results on the studies consistent with the interim data release plan in the approved PAS protocol or 522 plan. The guidance documents also include

information about posting important interim results on the program's web pages outside of an interim data release plan.

When interim data includes additional information that will be beneficial for public awareness in order to protect public health, FDA may also include relevant data on the program's web pages, regardless of an interim data release plan, including the PAS protocol or 522 plan.

The recommended elements to include in PAS protocols and 522 plans were also updated to include an interim data release plan. The guidance documents recommend that sponsors include in the interim data release plan the frequency and type of interim data analysis, data and points to be assessed and posted, and proposed frequency of posting on the FDA's website. The content of the progress and final report was updated to give an opportunity to sponsors to propose summary data to be posted on FDA's website. FDA will make the final determination of what information is posted based on the totality of our review and consistent with applicable disclosure laws.

I have given you a lot of information on the postmarket studies programs and updates to their guidance documents in a short period of time. In addition to the guidance documents and postmarket mandated studies programs databases, you can also go to the programs' web pages for additional information. Here is our team's contact information for any questions or comments you may have on the postmarket mandated studies programs.

In summary, postmarket mandated studies are important tools to ensure continued device safety and effectiveness. Updates to the guidance documents focus on activities to address postmarket questions in a timely manner. This included early and ongoing communication with manufacturers, collaborative establishment of PAS protocols and 522 plans, enrollment milestones and study completion timelines to ensure that the studies achieve objectives and are completed in a timely manner, and timely reporting, review, and public posting of postmarket study information.

This ends our presentation, and we thank you for your attention.

**CDR Kim Piermatteo:** Thank you, Erika, for that presentation. At this time, I'd now like to introduce our additional panelists who will be joining Erika for the live question and answer segment of today's webinar.

Dr. Daniel Caños, Director of the Office of Clinical Evidence and Analysis, or OCEA, within CDRH's Office of Product Evaluation and Quality, or OPEQ. Dr. Minerva Hughes, Regulatory Counsel within OCEA. Hina Pinto, Acting Deputy Division Director of the Division of Clinical Evidence and Analysis 1, specifically Clinical Policy and Quality within OCEA. And Dr. Megan Gatski, General Health Scientist on the Postmarket Programs Staff within OPEQ's Immediate Office.

Before we begin taking your live questions, I would like to go over a few reminders and tips. Foremost, to ask a question, please select the Raise Hand icon, which should appear on the bottom of your Zoom screen. I'll announce your name and give you permission to talk. When prompted in Zoom, please select that blue button to unmute your line and then ask your question. After you ask your question, please remember to lower your hand. If you have another question, please feel free to raise your hand again to get back into the queue, and I will call on you again as time permits. And lastly, please remember to limit yourself to one question only and try to keep it as short as possible.

Now as we wait to receive your questions, I'd like to welcome our additional panelists with a few questions we've received since the final guidances were issued.

For our first question, I'll be directing that to you, Daniel. Daniel, the question is, can you explain FDA's thinking around the enrollment milestones included in the guidance documents?

**Daniel Cños:** Hi, good afternoon. Certainly. The enrollment milestones included in the guidance documents are intended to be reflective of those that are most likely to result in successful study completion in a timely manner. They are recommended based on FDA's experience with postmarket mandated studies and the importance of timely postmarket data collection for ensuring continued device safety and effectiveness. The guidance documents encourage sponsors and FDA to work together to establish the post-approval study protocol or 522 plan, including enrollment milestones.

**CDR Kim Piermatteo:** Thank you, Daniel. Alright, for our next question, I'll be directing that to you, Minerva. Minerva, the question is, can you explain FDA's intent in posting interim data of postmarket mandated studies?

**Minerva Hughes:** Thank you, Kim. Thank you for that question. FDA posts information about postmarket mandated studies really to provide transparency to the different stakeholders. This includes consumers, health care providers, and industry at large. The guidance documents were updated to include that sponsors may propose summary data to be posted on FDA's website, but FDA will make that final determination. And in making that determination, we will consider the totality of the data that's available and ensure that anything posted is consistent with applicable disclosure laws.

**CDR Kim Piermatteo:** Thanks, Minerva. Now for our next question, I'll be directing that to Hina. Hina, the question is, what if my study is delayed and I want to request a change to the approved PAS protocol or 522 plan?

**Hina Pinto:** Thank you, Kimberly. Good afternoon, everyone, and thank you for joining us today. So to address that question, Kimberly, FDA does understand that study delays may sometimes occur. However, we generally do not intend for sponsors to routinely modify the post-approval study protocols or 522 plans to adjust those study milestones.

We would recommend that sponsors identify any missed milestones the causes for the delay or failure to meet the enrollment milestones and their plan to address those challenges and to meet the established milestones as part of their interim reports. We would also ask that sponsors communicate these circumstances which are impacting their ability to meet these study requirements to the FDA as soon as possible.

With that said, sponsors may request changes to the original enrollment milestones that are identified in the PMA approval order or the 522 plan if they believe that these requests are consistent with the recommendations outlined in the guidance. And these proposed changes to those enrollment milestones should be submitted as PMA supplements or a 522 study supplement, and they will be considered on a case-by-case basis. And these request, we would recommend that these requests not be combined with any other request for changes to the PAS protocol or the 522 plan.

**CDR Kim Piermatteo:** Great. Thank you, Hina. Alright. Megan, I'll be coming to you with our next question. Megan, the question is, will FDA communicate with the affected medical device company before issuing a 522 order?

**Megan Gatski:** Thank you for that question. Yes. Whenever practical or appropriate, FDA will engage with manufacturers prior to issuing a 522 order. When we assess the appropriateness of issuing the 522 order, we do recognize that engaging with external stakeholders may provide helpful additional contextual information to inform decision making. And when a 522 order is being considered for issuance at the time of market authorization, FDA may advise the manufacturer of the potential 522 order and the surveillance plan schedule.

**CDR Kim Piermatteo:** Thank you, Megan. Alright, our next question, our live question is coming from Rabia. Rabia, I have unmuted your line. Please unmute yourself and ask your question.

Rabia, I'm going to go ahead and ask you to unmute one more time.

**Rabia Sultan:** Oh, I'm sorry. I don't have any question. I'm so sorry I just did by mistake. Sorry.

**CDR Kim Piermatteo:** That's OK. Please lower your hand. Alright, our next question is coming from Eric. Eric, I have unmuted your line. Please unmute yourself and ask your question.

**Eric Eggers:** Hi, thanks for taking my question. Just a quick question on slide 20, regarding the 522 statutory criteria. Regarding criterion 2, the line expected to have significant use in pediatric populations, is that based on some absolute number, or is there some kind of threshold that you're looking to trigger that? Thank you.

**CDR Kim Piermatteo:** Thank you, Eric, for that question. Minerva, would you like to take the first response?

**Minerva Hughes:** Sorry, you know, thank you, Eric, for that question. There isn't a fixed number around expected this. I think you're going to get significant, which is always a trip when it comes up. But oftentimes, many of the products that would be getting 522 are generally would be indicated for the pediatric population.

So your question around threshold is, no, there isn't one that we're relying on. But it's generally fairly clear if you look through our database on the types of 522 studies that would involve pediatrics why that would come up and be the case for that intended use, for that particular use.

**CDR Kim Piermatteo:** Thank you, Eric, for that question. And thank you, Minerva, for that response. Our next question is coming from Marysa. Marysa, I have unmuted your line. Please unmute yourself and ask your question.

Marysa, are you able to unmute your line?

**Marysa Loustalot:** Hi, yes. Thank you. I have a question in regards to the milestone expectations and keeping in mind a least burdensome approach in terms of the commitments for enrollment reports and progress reports and things like that.

If a sponsor is looking to make protocol changes to increase enrollment, let's say a milestones have been missed, a PMA supplement is required for a protocol change. However, if we also need to update those milestone dates in regards to the protocol changes, would we include that in the same PMA supplement as a protocol change? Or would the milestone update need to be included in the enrollment status report?

**CDR Kim Piermatteo:** Thank you, Marysa for that question. Erika, I would like to come to you. Would you like to start with this one?

**Erika Tang:** Yes, thank you. When the study is being delayed, and you want to look into changes in the enrollment milestones, we recommend that you inform us first in enrollment milestones, and we-- I'm sorry-- in enrollment status reports. And with the team, the review team, you can discuss how the studies can be improved enrollment milestones, and also the work with a mitigation plan. And we can recommend later if a PMA supplement will be needed. Does anyone else have anything to add?

**Hina Pinto:** Sure. I'm happy to add a couple of comments here as well. Thank you for your question. As I indicated in the previous response to my question around changes to the approved protocol and 522 plans, we certainly want to make sure that the sponsor is engaging with the FDA as early as possible to inform us of the delays that are happening so we can work with you, as Erika said, on any mitigation plan that's needed. Whether that be increasing the number of enrollment sites or thinking in a different way to address the study questions. And so certainly contact us early, and provide, if you've already thought about it, provide your mitigation plan in your reports. And then we will work with you on the enrollment milestones.

It may not be that the enrollment milestones need to be updated for every situation. And as I mentioned, we do anticipate these being in limited circumstances where the enrollment milestones would need to be updated. But we are certainly willing to work with you to make sure the study stays on track and gets on track if it is delayed.

**CDR Kim Piermatteo:** Thank you, Marysa, for that question, and thank you Erika and Hina for providing a response. Our next question is coming from John. John, I have unmuted your line. Please unmute yourself and ask your question.

**John Whatley:** Hello, can you hear me?

**CDR Kim Piermatteo:** Yes, we can.

**John Whatley:** Yes, so this is a simple question. So I have a project that's absolutely a new novel device that's pretty much come on the horizon where the FDA. And it's an example, I could say, this new device that's going to link the brain to a computer via interface, which is a device. So I'm curious to know, would the FDA consider allowing additional time to respond or tweak their studies? Because the fact that this is new not only to the FDA, but also new to manufacturers. It's a device never seen before.

**CDR Kim Piermatteo:** Thank you, John. Very interesting question. I will turn that over to Hina to provide you with a response.

**John Whatley:** Thank you.

**Hina Pinto:** Thanks, John, for your question. In those circumstances, we would say that we would really recommend contacting the OHT that would be reviewing the device and starting these conversations early to make sure that everybody understands what the device is, there's agreement on what testing may be needed to support premarket review of that particular device, as well as whether there are any considerations that need to be made on the postmarket setting.

And so I would certainly say start early in your engagements with the OHT. And during those conversations, I think hopefully things will be clear. And so we can continue to ensure that these postmarket questions, if need be, are addressed in a timely way. But I think it would be product specific and circumstance specific as well.

**John Whatley:** Thank you.

**CDR Kim Piermatteo:** Thank you, John. And thank you, Hina. Alright I'm going to go back to Erika regarding a question that we had previously received. And Erika, that question is, can you explain the difference between PAS enrollment status reports versus PAS progress reports?

**Erika Tang:** Thank you, Kim, for that question. Yes, in an enrollment report, the enrollment report should provide the progress towards meeting the enrollment milestones per the approval orders. And it should include sufficient data for FDA to track the progress towards the study enrollment milestones. And the guidance document specifies the recommended content for enrollment status reports.

Whereas a PAS progress report should describe the status of the PAS prior to its completion. And this includes the subject accountability, as well as device performance and safety and effectiveness data. And the submission of the interim report should be based on the schedule set in the PMA approval order.

**CDR Kim Piermatteo:** Great. Thank you, Erika. Our next live question is coming from Charles. Charles, I have unmuted your line. Please unmute yourself and ask your question.

Charles, are you able to unmute your line?

Charles, I'm going to give you one more opportunity to unmute your line and ask your question.

Alright, Charles, if you have a question, please go ahead and raise your hand again and get back into the queue and I'll call on you as time permits.

At this time, I'm going to go back to one of our other previously submitted questions, and I'll be directing this one to you, Hina. The question is, how does FDA recommend that sponsors meet the timeline for submission of PAS protocols after PMA approval?

**Hina Pinto:** Thanks, Kimberly. I think as you've heard a number of times today, we would encourage early and ongoing interactions between sponsors and FDA staff to establish a PAS protocol. This would ideally be finalized at the time of PMA approval.

However, even in circumstances when a post-approval study protocol is not finalized and approved with the PMA, engaging with FDA early to understand the study requirements and to discuss the enrollment

milestones and study completion timelines prior to that PMA approval really will help sponsors to develop their PAS plan and to address the post-approval study objectives in a timely manner.

**CDR Kim Piermatteo:** Thank you, Hina. Alright. I'm going to, if anyone has a question, please be sure to raise your hand so I can unmute your line and you can ask your question. Erika, I'm going to come to you with another previously submitted question. That question is, on the FDA programs databases, why are some studies identified as progress adequate while others are identified as ongoing?

**Erika Tang:** Thanks, Kim. Yes, submissions received on or after the guidance documents publication date, they are assigned updated study status categories. Whereas the former studies status categories will be used for those files received prior to the October 7th, the final guidance documents publication date.

So this is the reason that the stakeholders will see current and former study status categories during an interim period on the PAS and 522 program web pages. And this will be until new information is submitted to FDA for our review and the study status category is changed.

**CDR Kim Piermatteo:** Thank you, Erika. Alright, I'm coming back to Charles. Charles, I've unmuted your line. Please unmute yourself and ask your question.

**Charles M:** Yes, I found it. Thank you.

**CDR Kim Piermatteo:** Great.

**Charles M:** I haven't used Zoom for a couple years. So anyway, thank you for answering my question. Here it is. In my opinion, the risk management also is a live document. Now, when you create it-- when you create the PAS report and there is adverse effect to it.

So will you need to really be traceable as well to the risk management? What I'm saying risk management becomes invalid because it's not traceable enough anymore to really what's going on with the device or with the drugs. I just want to see your opinion if I am correct on this or not.

**CDR Kim Piermatteo:** Thanks, Charles. I think could you-- I think we would like for you to further clarify your question. Could you repeat just what your question is?

**Charles M:** Yes. When you write a report, PAS report, does it have to be traceable to the risk management as well? So will be traceable, so we have to update the risk management of the device as well to be making sure the risk we see, actually, it is also as a part of the risk management mitigation.

**CDR Kim Piermatteo:** Thank you, Charles, for clarifying.

**Charles M:** Thank you.

**CDR Kim Piermatteo:** Thank you. Hina, would you like to start with a response?

**Hina Pinto:** Sure. Happy to. Thank you, Charles, for clarifying that. I think your question probably relates to the larger topic of quality system and risk management. What I will say as it relates to post-approval studies or 522 studies is that we do work with the sponsors to consider the entire benefit risk profile of

the product when requiring a post-approval study as a condition of approval or when we're issuing a 522 order to address some postmarket questions around the device.

And so that is certainly taken into consideration at that point. If there are specific risks that arise based on the information that's being collected, we do think that please make us aware of those, either through the progress reports, or if the risk is significant, then reach out to the OHT that's reviewing the device.

So hopefully, that helps address your specific question as it relates to PAS. But you may also have a general question related to quality system or risk management that may be outside of the scope of this particular session here.

**Charles M:** Thank you. I appreciate that. That will answer my question. Thank you.

**Hina Pinto:** You're welcome.

**CDR Kim Piermatteo:** Thank you, Charles. And thank you, Hina. And Charles, just keep in mind, we did just have an Industry Basics Workshop that discussed a lot about risk management. So that's available on our website on CDRH Learn, if you're interested in looking that up as well.

**Charles M:** Of course. Thank you. I appreciate it. Thank you.

**CDR Kim Piermatteo:** Sure. Alright. At this time, I do not see any more raised hands, so I will make a call out. Does anyone have a question that they would like to ask our panelists today?

OK, seeing none, I would like to thank you all for a very informative question and answer segment. And I'd like to turn it back over to Erika today for her final thoughts. Erika…

**Erika Tang:** Thanks, Kim. And thanks for all your great questions, everybody. And we really appreciate it. And I would like to highlight that the timely data collection in postmarket mandated studies is needed to ensure the continued device safety and effectiveness. And as we have been mentioning the early and ongoing collaboration between FDA and sponsors to establish the PAS studies protocols or 522 studies plans, and this includes the enrollment milestones. It's essential to meet this objective.

And we encourage you to contact us through our mailbox, the MandatedStudiesPrograms@fda.hhs.gov with any questions you may have on the PAS and 522 studies or on the final guidance documents. You can also contact the Offices of Health Technology, or OHTs, to discuss your device potential postmarket evaluation needs. And we really thank you for your time and for joining us during today's webinar. Back to you, Kim.

**CDR Kim Piermatteo:** Thank you, Erika, for those final thoughts and for your presentation today on these final guidances. And I'd also like to thank Daniel, Minerva, Hina, and Megan for their participation in today's webinar.

For your information, printable slides of today's presentation are currently available on CDRH Learn at the link provided on the slide under the section titled “How to Study and Market Your Device,” and then the subsection titled “Clinical Studies and Investigational Device Exemption or IDE.”

A recording of today's webinar and a transcript will be posted to CDRH Learn under this same section and subsection in the next few weeks. A screenshot of where you can find the webinar materials has been provided on the slide as well.

If you have any additional questions about today's webinar, please email us at DICE@fda.hhs.gov. And we also encourage you to attend a future CDRH webinar. And a listing of all of our upcoming webinars is available at www.fda.gov/CDRHLearnWebinar.

This concludes today's CDRH webinar. Thank you all again for joining us and have a wonderful day.

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