

**FDA Webinar-Regulatory Overview for Developers and Sponsors of Neurological Devices:  
An Introduction to Premarket Approvals  
Moderator: Irene Aihie  
July 26, 2016  
1:00 pm ET**

Coordinator: Welcome and thank you for standing by. At this time, all participants are in a listen-only mode until the question and answer session of the call. To ask a question during that time please press star followed by number 1.

Today's conference is being recorded. Any objections you may disconnect at this time. Now I'd like to turn over the meeting to Irene Aihie. You may begin.

Irene Aihie: Hello and welcome to today's FDA Webinar. I am Irene Aihie of CDRH's Office of Communications and Education. As a part of the FDA's ongoing effort to assure patients and providers have timely and continued access to safe, effective, and high quality medical devices, today's Webinar will provide developers and sponsors of neurological devices, information on the pre-market approval process.

The pre-market approval is the most stringent type of device marketing application required by the FDA, and is required because of the level of risk associated with Class III devices.

Mike Hoffmann, Deputy Director of Regulatory Policy for the Division of Neurological and Physical Medicine Devices in the Office of Device Evaluation here in CDRH will start today's presentation. He is joined by members of the Division.

Following the presentation, we will open the line for your questions related to information provided during the presentation. Additionally, other center subject matter experts will join the team to assist with the Q&A portion of our Webinar. Now, I give you Mike.

Mike Hoffmann: Welcome. Good afternoon. We're glad you could join us to hear some information about the PMA process.

Just to give you a quick idea of the agenda that we're going to go through today, we're going to give some quick introductions to the PMA process, provide information on how sponsors and principle investigators can move their products to market, some information on clinical testing, non-clinical testing, post-approval studies, bioresearch monitoring, and then the question and answer session.

Again, I am Michael Hoffmann. I'm the Deputy Director for the Division of Neurological and Physical Medicine Devices in the Office of Device Evaluation here at CDRH.

We usually - we like to start our presentations where we emphasize everything which is, that the CDRH vision. And while I'm not going to read through each of the aspects of our vision statement, we do want to highlight the first one which is, that patients in the U.S. have access to high quality, safe and effective medical devices of public health importance, first in the world.

And also, to start at the beginning of what actually is a medical device? So, a medical device is defined in the Food, Drug, and Cosmetic Act. And it is defined as a device, meaning that it is an instrument; an apparatus, implement machine can drive its implant, etcetera, intended for use in the diagnosis, cure, mitigation or treatment or prevention of disease in man. And is intended to affect the structure or function of the body in man and, does not do so through chemical purposes or through chemical actions.

So, we do have a wide array of regulatory processes, and we review a wide array of medical devices which have different risks and different benefits. And these different processes are used to match up with those different types of medical devices that have those different risks. And we use the most appropriate pathway and regulatory process for those - for each device.

Today we're going to be focusing on the PMA process which is highlighted at the top of the screen. And as mentioned before, that is the process that we use for the highest risk devices that we review.

This slide gives several examples of neurological products that we regulate here at CDRH. They include everything from brain stimulation - deep brain stimulation devices to neurovascular devices to neurosurgical devices to diagnostics as well.

And here we want to focus a little bit more on some of the other specific devices that we have cleared and approved here. And they range from clot retrievers, prosthetic arms. And what also wanted to note here is, we have ablation therapies as well that have gone through the PMA process.

Not all of these have gone through the PMA process. Again, we match up with the appropriate risks and mitigations and make sure that we use the appropriate pathway for each one.

I'll now turn it over to Tim, who's going to talk more about the regulatory requirements.

Tim Marjenin: Hi, my name is Tim Marjenin and I'm the Chief of the Neurostimulation Devices and Neurology Branch. And over the next few slides I'm just going to give a very high level discussion of some of the regulatory requirements for PMA application.

This is going to be fairly high level. Each individual piece could probably take up at least an hour.

So just by way of explanation, more information is available in CDRH's Education Page, CDRH Learns. This is also part of Device Advice which is a comprehensive collection of information that covers practically everything about our regulatory processes.

So, let's start with the basics, the pre-market approval statute in the regulation. The statute can be found in the Food, Drug, and Cosmetic Act, Section 515. And that's what establishes the general requirement for PMAs in the regulations and the CFR that corresponds to 21CFR Part 814.

I would like to point out that some of you may be familiar with the Humanitarian Device Exemption which is also - which is actually contained within 814. However, that's not going to be covered as part of this Webinar here today.

Relative to other submission types, there are a lot of differences when it comes to PMAs. And when you're thinking about whether it be a 510(k) or even a de novo, there's a lot more that's involved with a PMA.

So, for example there's a Safety and Effectiveness Standard. And we're not talking about substantial equivalence here. You have to demonstrate that the device has a reasonable assurance of safety and effectiveness.

There are also post-market requirements in the form of annual reporting and, types of submissions related to manufacturing changes.

The review process is a little bit different too, especially when it comes to original PMAs or Panel-track supplements. You have a filing review which is something that's not typically found on other types of submissions, as well as, a manufacturing review which is also not found on other types of submissions. Post-market requirements can also sometimes include a post-approval study.

There are two main types - two main ways of submitting a PMA. One being the traditional route and one being a modular PMA. Traditionals are more common than the modulars.

And so traditionals, you submit the complete application all at once to FDA, at which point the review begins on all of that information.

With a modular PMA, however, the contents are broken down into various pieces and parts and are submitted over time. And the final module that is submitted would be the clinical module at which point everything gets created into one single, original PMA and the review continues.

So, modular review may or may not suit your needs. It's going to largely depend on what - on whether you think it is appropriate and feasible for you. And really, make sure that you understand the implications and the timelines that are associated with modular review. And please feel free to ask questions if you're not sure about anything related to that.

There is a Guidance document. The link is here at the bottom of the slide. I highly encourage you to review that if you are interested in the modular process.

When it comes to the actual review process of an original PMA the - some detailed information can be found again, at Device Advice with the link here.

So, there are some important timeframes to consider at the front end. First off, there's a Refuse to Accept review. Those of you who are familiar with the 510(k) process, it's largely the same sort of thing. Although, there may be some slight variations in the types of things that we're looking for.

Filing review is something that's not found on other types of submissions other than HDEs, and that happens within 30 days of receiving the file.

And then the substantive review is ongoing up through the first 90 days of the review of the file after we receive it.

So, when you're talking about the substantive review that ends with the substantive interaction decision point, and that occurs by Day 90. It can happen before; no later than Day 90. And at that point we will either request some additional information or we'll determine that there are only minor questions and that those can be addressed interactively.

So, if we're going to request additional information by letter, then we're going to outline what all of those questions are. And we're going to tell you why we need - what's missing, what needs to be changed, and why we need that information.

And so, at that point the clock stops and the ball is in your Court until you address all of those questions. If we continue, because there are only minor questions, the clock doesn't stop and we try and resolve everything interactively.

So, after the substantial interaction decision point, let's say that either we continue interactively or you send in a response to the letter that we sent you, we will work interactively with you to resolve all remaining questions.

You should be prepared for multiple interactions about things like labeling or the Summary of Safety and Effectiveness Document; the SSED. And if there's a Panel meeting that's scheduled, it will likely occur after the substantive interaction decision point.

Very briefly, about Advisory Committee input, better known as Panel, so this is defined in Part 814. And it says that, FDA will begin substantive review of a PMA after it is accepted for filing. And we may refer the PMA to Panel on our own initiative. And we will do so upon the request of an applicant unless we think that - well it would really duplicate what's been done previously by the Panel.

And so the Panel's input, just to clarify, is a recommendation. It's really no different in the most basic terms, from getting input internally from other members of the team. It's just done much more publicly and there's much

more work involved with it. So the FDA is the one that makes the final decision on the PMA.

Once a PMA is approved there are a number of different types of changes that can be made. And depending on the type of change, the nature of the change, there are different supplements that are submitted and reviewed in order to get those approved and into commercial distribution.

Panel track supplements are closest to the original PMA. They are - they can involve Panel meetings, but they don't have to. It's really for when you're changing the indications. You might be adding a new indication for use to an existing PMA. A 180-day supplement are for fairly significant changes to an existing device.

Real-time reviews are slightly less significant changes. They have their own guidance document. Thirty day notices are related to manufacturing changes. That also has its own guidance document.

And there's one on here that I'm not going to be able to spend a whole lot of time on called, Special Supplement Changes Being Affected. And basically that's for labeling changes that a company wants to make to help make a device safer.

So there is a guidance that covers all of the different types of modifications that could be done to a PMA, and the associated supplement types that go along with those.

And so with that I'm going to turn it back over to Mike to talk about how sponsors principle investigators move their product to market.



Mike Hoffmann: Thank you Tim. So as Tim mentioned, there is the - one of the differences in the PMA process is the Safety and Effectiveness Standard. So that's where we have our definition of safety.

So there is a reasonable assurance that a device is safe when, if based on developed, scientific evidence, the probable benefits of the device, or its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, it outweighs any probable risk.

For effectiveness there is reasonable assurance that a device is effective if, based on valid scientific evidence, in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.

So there are a lot of terms in there. And one of those is, valid scientific evidence. So FDA relies on valid scientific evidence to determine whether there is reasonable assurance that a device is safe and effective. And there are several different sources of valid scientific evidence according to the regulations, including well controlled investigations, studies, and objective trials without mass controls.

Well documented case histories conducted by qualified experts, and reports of significant human experience with the marketed device.

However, since these Class III devices which we review under PMAs are our riskiest devices, we rely heavily on well controlled investigation. And to be a well-controlled investigation the plan or protocol for the study and the report should include the following.

A clear statement of the objectives of the study. A method for selection of the subjects that includes the following.

Adequate assurance that subjects are suitable for the study. Minimization of possible bias. Comparability between the test groups and in control groups. As well as, an explanation of the methods and observations of recordings and results that were used. A comparison of the results of the treatment or diagnosis with a control, so that there is a quantitative evaluation. And a summary of the methods of analysis, and an evaluation of the data derived from the study including any appropriate statistical methods utilized.

So there is a lot in the definition of a well-controlled study. And we have a very good system of getting feedback from FDA to determine how suitable your proposed investigation will be to support a future PMA.

And the best way that we have to do that is our Pre-submission Program. And there's a guidance that is, you know, in which we strongly encourage you to review and to take advantage of.

I'll now turn it over to Stacie who will begin a discussion about the non-clinical testing.

Stacie Gutowski: Thank you very much Mike. I'm happy to discuss the non-clinical testing with you today.

So non-clinical testing is also known as pre-clinical testing and it encompasses all testing conducted outside of a human subject. So this will include performance and bench testing which can include standards, as well as, any animal testing that you use to support a PMA.

Common non-clinical tests include electrical safety, battery reliability if applicable, if your device has a battery. Electromagnetic compatibility including MR compatibility. Biocompatibility, sterility and shelf-life testing, software testing, general, other engineering tests, as well as, GLP-compliant animal studies.

And for further information regarding any of these types of tests, you can look at our guidance document database, as well as, our recognized consensus standards database to see what standards the FDA recognizes in support of our device submissions.

Other performance testing can include device specific tests which may or may not have specific guidance documents, depending on which device you are submitting. And you should always check our databases as listed on the previous slide for information about guidance documents and standards.

General examples of this type of other performance testing includes functional testing to demonstrate that the device will function as it is intended. Mechanical testing, fatigue testing, coating integrity should that apply to your device, and others as needed.

Considerations for non-clinical testing include that the test devices should be in the identical final, finished form. So that means that you'd use the same manufacturing processes, materials, equipment, environment; etcetera. And the devices should also be post-sterilization processing to demonstrate that the sterilization that you plan to use does not alter the performance or outcome of the device.

And if the test device is not identical to the final finished form, you should definitely provide justification as to why that has not been done.

Additional considerations include that you should provide full test reports. This may not apply when testing is completed in accordance with different standards. But in general, summary reports do not always provide sufficient details for us to review.

Our testing and compliance with these FDA recognized consensus standards should always be accompanied by a Form FDA 3514 to describe your compliance with these standards.

Testing to alternate standards is definitely not advised if there is a corresponding FDA recognized standard in the database.

At this point I will pass it on to Sam who will talk about post-approval studies.

Sam Raben: Thank you very much. During the review of the PMA, FDA may request a post-approval study be conducted as a condition of approval. This study request is to assure continued safety and effectiveness of the approved device.

These studies can be clinical or preclinical evaluations and may request long-term safety and effectiveness information that could not be addressed by premarket data.

Post-approval clinical studies may be new studies with a new cohort of patients. Or continuation of follow-up of patients enrolled in the investigational device exemption or IDE clinical study.

We strongly encourage applicants who are conducting a pivotal study to consent subjects for long-term participation in the study such as five years, in

the event that long-term safety and effectiveness data may be needed as a condition of approval for the PMA.

Before a PMA is approved, and during the review phase, if a post-approval study is needed, FDA will provide the applicant with the general framework for the design and endpoints of the post-approval study. And concurrence will be obtained from the applicant agreeing to this general framework for the post-approval study.

The full and complete post-approval study protocol can be either, developed and agreed upon by FDA and the applicant during the PMA review process if there is time or, this information can be submitted after the PMA is approved, through a PMA supplement.

If a post-approval study is warranted, development and agreement on the study protocol should be provided by both FDA and the applicant. A post-approval study protocol should include the following.

A background section that includes the regulatory history, device description, communication for use. The purpose for the proposed study, the objective and hypothesis that will be evaluated. The trial design, the treatment population which should include information regarding the inclusion, exclusion criteria, as well as, the proposed comparative group.

A sample size calculation with accompanying statistical justification based on the study hypothesis, primary and secondary endpoints, the length of follow-up, including the follow-up schedule, baseline, follow-up assessment, a description of the data to be collected in the collection procedure, a statistical analysis plan, and the data collection forms such as the Informed Consent form, IRB Approval form, and the Case Report form.

A summary of the reported requirements for the interim and final reports.  
And finally, the study milestones and the outline of the study timeline.

For post-approval studies the applicant will submit interim reports every six months for the first two years and then annually, thereafter. The due date of these reports is based on the original approval date for the PMA.

These reports should contain an update of the study progress, a summary of the safety and effectiveness data, along with an interpretation of the study results to date.

At the conclusion of the study the final report should be submitted no later than three months after study completion. Study completion is defined as, all subjects having completed follow-up.

If you fail to complete a post-approval study, this may result in a withdrawal of the approved PMA. If there are limitations or a particular scenario under which it is determined the study cannot be completed, this information should be communicated to FDA as soon as possible, either through an interim report or a PMA supplement.

For additional information regarding post-approval studies, we provide the following links. The first is, FDA's guidance regarding post-approval studies and posed by PMA orders. This guidance document discussed the study protocols, interim report procedures, and final report documentation.

There is also logistical information that may be beneficial during the development and conduction of the study.

The second link is the post-approval study public database. This database provides general status information regarding post-approval studies ordered since January 1, 2005.

And then finally, FDA - the final link is for FDA's Post-Approval Web site which provides some more general information regarding post-approval studies, as well as, some additional links and resources.

And then with that I will turn it over to Commander Bah.

Isatu Bah: My name is Isatu Bah. I'm with the Division of Bioresearch Monitoring.

The BIMO Program is a comprehensive agency-wide program of on-site inspections and data audits designed to monitor all aspects of the conduct and reporting of FDA regulated research.

Clinical studies are conducted all over the world. We receive data from foreign countries for pre-market approval application. We therefore conduct domestic, as well as, foreign inspections. We conduct inspections anywhere the device study records are maintained.

We have these three objectives and one way we meet them is through inspections. The purpose of inspections is not to find errors, but to gain confidence in how the study was conducted. And to gain confidence in the accuracy, reliability, and integrity of the submitted data.

Its involves interview with the site personnel, onsite evaluation of source documents, and the evaluation of the systems in place to protect human subjects, produce quality data, and to comply with applicable regulations.

For PMAs, the FDA investigator who is doing the inspection will do a sampling of data and compare the data line listings submitted by sponsors in the PMA to the source documents and the case report form for accuracy and completeness.

These are the lists of regulations that are applicable to drug, devices, as well as, biologics.

These regulations are applicable just to device clinical studies.

These are some of the information that BIMO reviewers will review and consider when we do site selections for inspections. We also collaborate with the review divisions and the Office of Surveillance and Biometrics when we do site selection.

For PMAs, we have 30 to 45 days to issue inspection assignments. The FDA investigator at the District Office will usually contact the site personnel and notify them of the inspection between 3 to 5 days for routine inspections.

Please note that for “For Cause” inspections, we don’t preannounce the inspection. The FDA investigator may just show up on the site.

When the investigator arrives at the site, they will issue what is called the Form FDA 482, which is the Notice of Inspection. They will interview site personnel about their responsibilities in the conduct of the study.

They will review the study records and conduct data audit, comparing the data line listings submitted in the PMA to the source documents and case report forms.



If there are any deviations from the regulations, the FDA investigator will list that on the Form FDA 483 at the completion of the inspection. And they will discuss verbally, minor observations that may not be too egregious to list on the Form FDA 483.

These are some of the documents that the FDA investigator reviews during the inspection. The link at the bottom of this slide is for the Compliance Program Guidance Manual which is the CPGM.

The FDA investigators usually use this CPGM. It provides them with instructions to evaluate industry activities when conducting inspections.

This CPGM has been made available to the public through the Freedom of Information Act. Sponsors and industry can use this to prepare for future FDA inspections.

If a Form FDA 483 is issued, we usually recommend that the firm provide a response to the FDA investigator during the inspection or they can mail or forward it to the investigator within 15 days after the completion of the inspection.

We also highly recommend that you document any corrective and preventive actions. And make sure to include documentation of staff trained including dates and signature of staff that completes the corrective and preventive actions.

As well as, include the expected implementation dates for corrective and preventive actions.

At the completion of the inspection, the FDA investigator usually completes an establishment inspection report which is the EIR.

The FDA investigator will forward the EIR, the Form FDA 483, if it was issued, and any supporting documents to BIMO. BIMO will review the supporting evidence, the EIR, and the response if it was received within 15 days. And the BIMO reviewer will then determine the final compliance action.

These are the compliance classifications. For NAIs, BIMO will issue what we call, a Firm in Compliance Letter to the firm. For VAIs, BIMO will issue an Information Letter. And for official action indicated, we might issue an untitled letter, a warning letter, and we might recommend sanctions.

There are usually many opportunities for BIMO to collaborate with industry during pre-submission meetings, so that we can guide industries to conduct a successful study.

So please reach out; contact us during pre-submission meetings, and we can provide some guidance. And this is our information. You can reach us by phone or by email. Thank you. I now have Vesa.

Vesa Vuniqui: Thank you. My name is Vesa Vuniqui. I'm a Reviewer in the Division of Manufacturing and Quality, Office of Compliance, CDRH. During this presentation I'll be giving information on the manufacturing section of the PMA.

As an overview, Original and Modular PMAs, Site Changes, and 30 day Notices require manufacturing information for review. Some of these

submissions may also require pre-approval inspections. So I'll go over that as well, during this presentation.

Now I'll be discussing Original and Modular PMAs in more detail. First I'd like to discuss the major steps in the review of the PMA manufacturing information.

The manufacturing information is received in the Office of Compliance, in CDRH, and it is assigned to a Reviewer. This information is reviewed according to 21CFR Part 814 and Part 820.

Once a desk review is complete, if a determination for an inspection is made, the assignment is sent to the ORA, the Office of Regulatory Affairs.

ORA is then responsible for conducting inspection and complete the inspection report. That report is then sent back to CDRH for final review and classification.

There is a guidance document which is referenced on the slide that outlines the information that should be submitted for review. Primarily, this asks for submission of procedures and records for some of the subsections.

The information required is consistent with Part 814 and Part 820 and is divided into two sections, Design Controls, and Manufacturing Controls.

In order to facilitate the review process, it is recommended that the following be submitted with the application. A cover letter, overview of what the manufacturing section contains and how it is organized, device description, overview of the manufacturing facility, copy of the Quality Manual, and the list of standards used in the manufacturing process.

As mentioned before, the guidance primary asks for procedures related to major sections for design and manufacturing information which may include procedures related to complaint handling and CAPA.

It is also helpful, in addition to procedures, to include narrative summaries of the procedures, and then reference to the sections within the procedures or the location of the attached procedures.

Manufacturing information is required for all finished device manufacturing sites, including sterilization sites. So it is recommended, separate volumes be submitted, including procedures for each site.

CDRH Office of Compliance reviews the manufacturing section of the PMA according to the guidance document. If, during the review process, deficiencies are identified related to the quality system, they are communicated back to the applicant via a formal deficiency letter or email for a more interactive review process between the reviewer and the applicant.

Pre-approval inspections may be conducted at sites manufacturing finished devices, critical components, or sites performing sterilization. It is important to note in the submission, the date when the sites are ready for inspection as they are scheduled on or after that date that is identified by the applicant.

If however, the site is not ready for inspection, this may result in delayed approval of the PMA. This would be considered approvable pending GMP, so it's not a good position to be in. And so it should be avoided if possible.

A determination for inspection is made based on instructional history, and whether a similar process was covered during the previous inspection

conducted at the manufacturing facilities. This applies for both domestic and foreign facilities.

Now I'll move on to site change supplements. Site changes are appropriate when sites are not approved as part of the original PMA or PMA supplement. Or they were approved as part of the original PMA but, for the performance of different manufacturing activities.

There is a draft guidance of those previously issued for comment. It is very helpful and provides more details of when a site change is appropriate, and prediction of when an inspection would most likely be required.

The information required for a site change is similar to the original PMA manufacturing information. However, it does not require design control information since the design would not change.

It is important to provide process validation testing or state when the validations will be completed and when the site is ready for inspection.

Site changes are also subject to pre-approval inspection and follow the same time goal as the Original PMA. The same as the original PMAs, deficiencies related to quality system regulations are conveyed to the applicant via a formal letter or an interactive review process.

Now I'll give more information on 30-day notices. 30-Day Notices are appropriate when there is a manufacturing process change that would affect the safety or effectiveness of the device. This may include changes to the manufacturing procedure or changes to the manufacturing process or method of manufacture.

There is a guidance document that is very helpful and provides more details on when a 30-day notice is appropriate. And that is referenced on the slide.

Some examples of when 30-day notices are appropriate include, changing a manual process to an automated process. Changes to a cleaning process which is performed in manufacturing of the device. Change in machining lubricants, sterilization cycle, a change in sterilization cycle, or sterility dose auditing. Addition of manufacturing space or, addition of manufacturing lines at the same facility.

Changes that are not appropriate for a 30-day notice include addition of a new manufacturing site, or moving the manufacturing site. Changes a device design which includes changes to the design specifications. Or material changes and minor changes that do not affect the safety or effectiveness that are annual reportable.

After the review, an acceptance of 30-day notice can be made within 30 days. Or in cases when additional information is required, it can be converted a 135 day supplement.

It is common for deficiencies to be conveyed. But it's not important - but it is important to note, that the conversion can be done with or without deficiencies. After the review of the information within 135 days, the determination is made for approval or not approval of the supplement.

The information that should be submitted for a 30-day notice is a clear description of the change summary of the data or information supporting the change, statement that the change was made under requirement 520 of FD&C Act and, 21CFR Part 820, the reason for change including description and any adverse event or any failures being addressed.

And now I'll hand it over to Mike for closing remarks.

Mike Hoffmann: Thank you. Just a few quick items. So as mentioned before, we brought up the pre-submission process. It's a great way to get some feedback on your specific device; your specific issue that you would like to discuss with us so, it's very targeted.

You can use it to get feedback on an investigation that you're planning to conduct. You can also get information on an approach that you're going to take for a future PMA or a PMA that you're going to be submitting very soon.

We'd also like to point out that for information on some of the other regulatory processes and other items related to neurology and physical medicine devices, we have an article that's published in Neuron that we encourage you to look at, as well as, information about neurological devices from our FDA Web site that we have a specific link for here.

And we'd just like to leave you with, you know, basically what this is all about. We have several investigators; developers who are looking to bring high quality devices to patients. And they are the focus of what we do here. And what you all are doing as well. And thank you very much for your time.

Irene Aihie: Thank you. We're going to go ahead and open the line for questions. Just as a reminder, we will only be taking questions by phone. However there are a few questions here that have been typed in. I'm going to read those questions and see if anyone in the room would be able to answer them. But moving forward, we're only going to be taking questions by phone.

Okay, the first question that we have that was typed in was, what's the difference between RTA and billing review or filing review?

Tim Marjenin: This is Tim Marjenin. So the difference between acceptance reviews and filing reviews, acceptance reviews is something that was introduced with PMAs back in MDUFA III. It didn't used to be part of the review process.

And so it used to be that there was this filing review and then the substantive review. Really what the difference is, is that for acceptance, what we're looking at is whether the file is administratively complete. And that's true, whether it's a PMA or it's a 510(k).

A filing decision is really looking at whether the data are consistent with the protocol, the final device design, and the proposed indications. So it's almost like a light version of a substantive review. It's a little bit more targeted at something that you would along find with PMAs.

Irene Aihie: Okay. The next question here is referring to Slide 14. They said, FDA will issue a, refuse to accept within 15 days of receipt which is different from the PMA review process Web site. The link you provided states 45 days.

Was this a change that was adapted because of 21st Century Cures Act?

Tim Marjenin: So, with the PMA, they still go through the acceptance review, and that's going to be done 15 days after the PMA gets logged in. Meaning that it's passed through eCopy and it's actually been logged into the system.

And then within 30 days after that, we will conduct the filing review. So there's still two parts to the process. The first one being the acceptance review which happens within 15 days. And then 30 days following - within



30 days following the acceptance review or 45 days total, after the receipt of the PMA, that's when we would finish the filing review.

Irene Aihie: Thanks Tim. And then our final online question before we go to the phone, can you describe how the PMA process for a Class II device would differ from what was presented here?

Mike Hoffmann: This is Mike Hoffmann. It would differ quite a bit because if it's a Class II device, actually we have a different process for those devices.

So one of the earlier slides we mentioned that there are a host of different regulatory processes. And depending on what the risk of the device is, we will be able to find the most appropriate process and pathway for that device.

For a Class II device, the most often used process is our premarket notification or 510(k) process. There is more information about that in our Device Advice on line. But that is a different process.

Irene Aihie: Thank you Mike. Operator, do we have any questions on the line?

Coordinator: Not at this time. But as a reminder, please press star 1 to ask a question.

Irene Aihie: We'll give it a few seconds for folks to come in.

Coordinator: Our first question comes from (Frances Dillon). Your line is open.

(Frances Dillon): Hi, I have two questions. In regard to the refuse to accept period of 15 days, is this also applicable for a 30-day notice? And so would that mean that the 30-day notice period starts after the 15 day period?

And the second question is, is there any guidance regarding the submission content for a 180-day supplement?

Tim Marjenin: This is Tim Marjenin again. So I don't believe that there is a specific guidance document for 180-day supplement. In general I would tend to say that really, it needs to contain sufficient information to support the change that's being made.

So all of the testing that's being conducted, the protocols, the results, summary reports, any associated labeling if it's something that would be changing the labeling; those sorts of things.

Then as always, it's the sort of thing where if you have questions about whether or not you should be including a piece of information or you're just not sure about what you should be including, please feel free to reach out to somebody within the Division. Because that can be a simple 10-minute phone call where you just kind of quickly say, well here's what I want to do. Here's what I'm planning on providing. Does that sound about right? And we can help guide you.

As far as the RTA process, the RTA process applies to two types of PMA submissions. One is the original PMA and the other one is the Panel-track supplement.

All of the other supplements - all the other available PMA supplements do not have an RTA review.

(Frances Dillon): Okay, thank you.

Coordinator: The next question comes from (Richard Russo). Your line is open.

(Richard Russo): Thank you. Does the branch have any guidance or history with removable devices in contact with the CNS?

Irene Aihie: One second while we get that answer for you.

(Richard Russo): Thank you.

Mike Hoffmann: This is Mike Hoffmann. I don't think we can talk about specific submissions or specific devices at this time. I'm trying to think offhand. But that might be a better question that we can have either with (unintelligible). Or if you want to follow up with us after the Webinar, that's something that we can address off line.

(Richard Russo): Okay, thank you. And a second question if I could, will the agency, except for let's say a spinal cord application, the same data that it would accept for a cranial application? Or will you require different data for those two different anatomical sites? Biocompatibility data; excuse me, to be specific.

Mike Hoffmann: So this is Mike Hoffmann again. That's probably a question that's best reserved for a Q-submission. In general, when we are looking at I would say, the context of use or where a device is being used, we'll look at all the - any of the differences. And if there are similarities, we can see what we can do. But the best would be to use a Q-submission to get that information.

(Richard Russo): Thank you very much.

Coordinator: Our next question comes from (Chey Jerrell).

(Chey Jerrell): Yes, thank you. I just have a question in regards to possible permeation of the significant risk IDE PMA pathway. It's more of a just an intellectual - a thought experiment.

But I'm assuming it would be possible that you could have a significant risk IDE that ultimately could lead to a 510(k). Or is it the case that every significant risk IDE, ipso facto, will require a PMA?

Tim Marjenin: This is Tim Marjenin. So we actually come across that sort of thing all the time. And the short answer is, no. Just because it's a significant risk device and requires an IDE that does not automatically imply that it's going to require a PMA.

(Chey Jerrell): Okay, thank you.

Coordinator: Our next question comes from (Patrick Gora). Your line is open.

(Patrick Gora): Thank you. I've just got a quick question about manufacturing inspections. Our device is going to be a drug device combo. And so we're going to actually be going (unintelligible) photodynamic therapy device.

So I know you were talking about inspections at the manufacturer for the device portion. I don't know if you can answer this, but would that also include probably inspections at the drug manufacturer as well?

Vesa Vuniqii: I think that's slightly different. Because I think we're now talking about combination products. I'm not very familiar on how CDER - how they determine how they're going to conduct inspections or when they conduct inspections at their manufacturing sites.

Part of the combination product, I can tell you is that they consult CDRH for the device portion. And during that review we may recommend to CDER that they do part of that inspection. That they also cover medical device regulations.

(Patrick Gora): So yes, so you would - for your site then you would recommend or not recommend for whatever reason, to do the inspection of the device manufacturer.

But do you guys have any experience on the combo product Panels where they would also do an inspection at the drug manufacturer? Or would that be something that was very common or automatic?

Vesa Vuniquei: Again, this would be for the combination product manufacturer. So if there's a drug manufacturer by itself, then there's no devices - devices would not be covered during that inspection.

(Patrick Gora): Okay.

Coordinator: Our next question comes (Deanna Hunt). Your line is open.

(Deanna Hunt): Hi, thank you. I have two questions. The first, with regard to novel devices that are categorized as Class III devices by default, are these automatically considered significant risks? And would they require an Advisory Panel typically?

Tim Marjenin: So if I'm understanding your question correctly, and feel free to correct me. When you're talking about a novel device, it used to be back in the day, that it would automatically be Class III.

And so part of the issue that we came across was that not everything would be - would rise to the level of requiring a PMA due to the risks associated with it which is, why we have the de novo process for things that have less risk.

So I mean the - a novel device could be PMA or it could be a de novo, depending on the level of risk that's involved. And again, that's the sort of thing that's best discussed in the context, or at least introduced in the context of the Q-sub. And possibly in informational meaning just to come in and talk about what it is; what you have, and how it may be similar or different to other things that are out there.

As it relates to Panel input, historically we have tended to take first of a kind devices that are submitted via the PMA process to Panel. I believe that's still generally true.

Other times we - if it's the third or fourth one, we may or may not take something to Panel. Again, it's a matter of whether we've gotten sufficient input from the Panel in the past. On the same sorts of issues, there could be something unique about a new PMA, even if it is the third or fourth of a kind, that might necessitate take it to Panel.

That's the sort of thing that if there is the - if and when there is potential for taking something to Panel, that is something that's discussed with the sponsor. It's not all of a sudden out of the blue hey, there's a Panel Meeting and you should show up.

It's - we recognize and understand that there is a lot of work that's involved. And it's not a trivial decision to take something to Panel. So it's something that's discussed at length.

(Deanna Hunt): Okay, perfect. And the follow-up question to that, assuming we're dealing with a PMA device and putting together an IDE pre-submission, would it be possible or recommended to potentially combine you know, the different aspects of a study risk determination. A determination meeting; an agreement meeting, all within maybe a top level Q-sub pre-submission?

Or that the agency recommend to keep those individual elements broken up and keep them separated?

Tim Marjenin: I would say that in general, it may be possible to fold in aspects of a risk determination discussion into a traditional Q-sub. However, the output of a traditional pre-submission is not going to be the sort of thing that you could take back to your IRB and say hey, FDA has said that we have a non-significant risk device, for example. So it depends on what you need as far as that's concerned.

If you have more specific questions about that sort of thing, once again your best bet is to reach out to somebody with some more specifics and we can give you some more targeted feedback than we might be able to provide here.

(Deanna Hunt): Excellent. Thank you.

Coordinator: Our next question comes from (Michael Nelo).

(Michael Nelo): Hi. Thanks for the presentation. I just had a quick question. Does the Neuro Division have a stance on the amount of OUS versus US clinical data to support PMAs?

Tim Marjenin: We can and do accept OUS data. The amount - the relative amounts of data that's OUS versus within the US, that's not really something that's spelled out

anywhere in guidance saying that you need to have X percentage collected from within the US versus collected OUS.

I think really it's a matter of just ensuring that there's sufficient comparability between the two populations. And once again, running theme, whenever you have those sorts of issues and you have - and you are thinking about submitting a large proportion of OUS data in a PMA, it really is a good idea to come in and talk to us first, just to see whether there might be any particular issues that you need to consider when you're preparing a PMA application.

(Michael Nelo): Thanks Mike.

Coordinator: And our last question comes (Gregar Srivas). Your line is open.

(Gregar Srivas): Yes, (Gregar Srivas) speaking. We are doing MR safety testing, (unintelligible) Germany. And MR safety testing (unintelligible) we have a lot of active implant customers over from the new area. And quite often we recommend to do a test plan in advance.

And because the topic is quite complicated, I have heard from FDA already, and also we recommend in the very beginning to speak to FDA. And my question is, how do you propose recommending (unintelligible) to do this? Because quite often our clients are saying no, we don't like to speak to FDA in advance because they put more homework on our top than we may be actually have.

But we see quite often that they're doing a circle in approval if they do not use the full test plan and (unintelligible) right now.



Mike Hoffmann: And so this is Mike Hoffmann here. And so I would strongly advise that people come and use the pre-submission process.

I have heard that concern before about perhaps getting information you may not want to hear. I guess the real question tends to be, would you rather hear it beforehand when you have a chance to make some changes? Or would you rather hear it after testing has been completed?

And so I think after we explain that, I think people tend to have a better idea there. Because if you've already done the testing and we have some concerns with it; it may require retesting which may be more resources and more time.

Tim Marjenin: And this is Tim Marjenin. I've heard from other companies as well, that they do see the value in building some time into the development process to check in with us as necessary just because, as Mike was saying, it's far easier to figure out the type of testing that you need to do before you've actually done it.

And so the other aspect to that too is that, as much as we'd like to push the pre-submission process, and as much value as it can provide, it's not always necessary. And it's the sort of thing where if you're kind of on the fence as to whether it might be a worthwhile use of everybody's time -- yours and ours -- you can reach out to one of us and say hey, we're thinking about this testing.

And if you're doing it the same way as it's been done in the past; you're doing it to the standard. You're not really doing anything different. You don't really have much in the way of questions, we may say well, maybe that's not going to be the best use of your time, necessarily.

On the other hand, you could say well, we're thinking about doing it this way. And it is a little bit different. We think it might be okay. What do you think?

And so in that case we might say well, it's kind of up to you. It may be worthwhile to come in and have a chat with us about it first. If you think that you've got sufficient information from other sources, and you can adequately justify your position and why you believe that what you're doing is an appropriate approach relative to what else has been done, that's fine too. So, it depends.

(Gregar Srivas): Okay, thank you. So in total you think it's a good chance to save time on both parts, especially if there's a new device. And maybe the standard bandwidth of the standard word is developing itself in the meantime as well?

Tim Marjenin: Yes, I would say so.

(Gregar Srivas): Okay, thank you.

Coordinator: We have no further questions. I'll now turn the call back over to Irene.

Irene Aihie: Thank you. This is Irene Aihie. We appreciate your participation and thoughtful questions. Today's presentation and transcript will be available on CDRH Lean Web page at [www.fda.gov/training/cdrhlearn](http://www.fda.gov/training/cdrhlearn), by Thursday, August 3.

If you have additional questions about today's presentation, please use the contact information provided at the end of the slide presentation.

As always, we appreciate your feedback. Following the conclusion of the Webinar please complete a short 13 question survey about your FDA, CDRH Webinar experience.

The survey can be found at [www.fda.gov/cdrhwebinar](http://www.fda.gov/cdrhwebinar), immediately following the conclusion of the live Webinar. Again, thank you for participating. This concludes today's Webinar.

Coordinator: thank you for your participation in today's conference. Please disconnect at this time.

END