FDA Webinar:
Regulatory Advice for Investigators and Sponsors of Neurological Devices and the Path to Initiating Human Studies - Wednesday, September 14, 2016

Moderator: Irene Aihie
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Coordinator: Welcome and thank you for standing by. At this time all lines are on a listen only mode until the question and answer session. At that time, if you'd like to ask a question, you may do so by pressing Star, then 1 and recording your first and last name.

Today's call is being recorded. If you have any objections, you may disconnect at this time. I would now like to introduce your host for today's call, Ms. Irene Aihie. You may begin.

Irene Aihie: Welcome to today's FDA webinar. I am Irene Aihie of CDRH's Office of Communication and Education. As 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, we are hosting today's webinar to provide investigators, sponsors and new developers with information on the regulatory landscape for neurological devices.

This webinar is part of the FDA's partnership and the White House Brain Initiative focused on understanding the human brain and uncovering new ways to treat, prevent and cure brain disorders.

Dr. Carlos Pena, Director of the Division of Neurological and Physical Medicine Devices in the Office of Device Evaluation here at CDRH will begin today's presentation.

He is joined by members of the Division. Following the presentation, we will open up the line for your questions related to the information presented in today's webinar. Additionally, other center subject matter experts will join the team to assist with the Q&A portion of our webinar. Now, I give you Carlos.

Carlos Pena: Thank you, Irene. Good morning to all those on the phone. My name is Carlos Pena and I'm the director for the Division of Neurological and Physical Medicine Devices and I'd like to welcome you to our first FDA regulatory webinar for investigation sponsors of neurological devices.

This is a 90 minute session comprised of a couple parts including a brief primer on medical device review and regulation, non-clinical testing, early feasibility studies, and best practices on engaging with FDA.

Our goal is to brief all attendees on each of these points, but most important, sponsors and investigators obtain a sense of how to navigate the regulatory landscape of medical devices so that our landscape is more transparent, predictable and efficient and thereby assures patients and providers have timely and continued access to safe, effective, and high quality medical devices.

This webinar also supports, as Irene mentioned, our support of the White House Brian Initiative, which is focused on understanding the human brain. I'd also like to mention that this webinar is hosted not only by myself, but several talented staff in the Division of Neurological and Physical Medicine

Devices, one of the newest divisions at the Center for Devices and Radiological Health at the FDA.

So at the FDA, the vision of the Center of Devices and Radiological Health is that patients in the United States have access to high quality safe and effective medical devices of public health importance first in the world.

We take this principle seriously with urgency and we hope to show you how serious we are with some hard data at the FDA. A medical device where some background is defined as an instrument or apparatus, implement, machine or related article intended for use in a diagnosis or cure, medication, treatment or prevention of disease or intended to affect the structure and function of the human body and does not achieve any of its primary intended purposes through chemical action.

And so you might be saying, "Carlos, there are several provisos, addendums, clarifications. What really is a medical device?" And in short, if it diagnosis treats or prevents disease, it's a medical device.

It also does not achieve this purpose thought chemical action. And one can classify a device as a medical device even in the absence of change where the device impacts the structure or function of the human body.

We have been engaged in this technology sector some time. And this is a favorite slide of mind. Here I show you an array of products with neurological implications beginning with neurothrombectomy devices, epilepsy DBS, neurodiagnostics, prosthetics, therapeutic devices for migraines and micro catheters for the neurovasculature during surgery.

Many of these products treat diseases or conditions. The goal is not to discuss individual data in support of each device, but share with you here that each device went through a regulatory path that was in part tailored to the individual risk and benefit profile of the device.

And when other products may be targeted for the same indication or used in combination, we regularly, often, and without hesitation engage our colleagues in other product centers.

Medical devices are classified into class one, two, and three with regulatory control increasing from class one to class three. The device classification regulation defines the regulatory requirements for a general device type.

And so, for example, most class one devices are exempt from submitting an application to the FDA, most class two devices require pre-market notification, and most class three devices require pre-market approval.

We provide oversight across the three classes using tools known as general and special controls for which we helped communicate to sponsors and investigators to help them meet their regulatory obligations.

As mentioned in the last slide, medical devices can be classified into three types, two of which are listed here - class two and class three. And these higher risk classifications are linked to regulatory submission pathways.

For example, we receive several dozen PMAs each year. These submissions are the highest risk and typically require clinical data. These are class three. A second pathway is the 510k submission pathway.

And we receive several thousand each year. They typically do not contain clinical data, but are supported by non-clinical data and bench testing and review of prior submissions that may have contained these clinical data.

These are typically class two. And, finally, a third regulatory pathway is the general submission process, which includes devices that aren't comparable to anything on the market and present a low to moderate risk other than other types of devices.

Typically, once we have granted a De Novo, that particular product becomes the predicate for subsequent products, which can then move along the 510k pathway.

And De Novo submissions would be the subject of our next webinar early next year. Another question that might arise is when is clinical data needed, especially when human studies maybe need to be an issue and are significant advance investments by sponsoring investigators, which FDA realizes.

Typically for PMAs, clinical data is needed. For De Novo submissions, typically clinical data may be needed, but it may not always be needed. And for 510k submissions, clinical data is typically not needed, although there are cases where clinical data was submitted.

So you're probably thinking to yourself, again, "Carlos, there are a couple provisos, addendums, and clarifiers. How do we really find out what is needed?"

And my response is that you can request feedback on any of these questions through the use of processes with pre-submission, preferably before starting

the study or making any investment into your device technology development plan.

And we will return to this shortly when Tim Marjenin reviews best practices on how to engage EFDA. One very important step in making sure is making sure sponsors and investigators understand the options that are available to them to get their product to market and making very clear and transparent the regulatory landscape.

Here are several guidance documents that are relevant to neurological devices listed in two pre-submission guidance documents that allows for an opportunity for early discussion and feedback from FDA to early feasibility studies designed to (unintelligible) for pivotal clinical investigators and expedite the access regulatory pathways for device.

And I'd like to note that the approach to earning feasibility studies will be discussed also during this webinar by Erin Keegan and Devjani Saha. All the guidances are intended to verify as clearly as possible the considerations that should be addressed to hopefully move a product to market and ultimately to patients.

And FDA's considering additional guidance. I'm delighted to indicate earlier this year we released a draft guidance for public comment, not from (unintelligible) focused conducting clinical trials on medical devices targeting neurological disease progression and (unintelligible) patient outcome.

A knowledgeable guidance that aims for regulation to keep pace with innovations. Many paths to market include selecting simple data about a medical device.

And they usually occur under what's called an IDE or an Investigational Device Exemption. Comparable to the drug side of an IND, IDEs allow an investigational device to be used in a clinical study in order to collect safety and effectiveness data required to support a marketing submission.

Our FDA has 30 days to make a decision about any IDE and we strive to get an IDE up and running, because the faster you can get an IDE going safely in the United States, the faster you can collect the data that leads to submit and marketing the application to get the device to U.S. patients.

And before you get an IDE, we may ask for non-clinical data and Molly Ghosh and Dhanya Williams will be discussing with you our non-clinical requirements and recommendations next.

But first, I would like to show - share with you how serious we are about moving devices to patients. Here is a graph that shows decreasing timelines in getting a medical device study up and running.

In FY11, the needed time to get full approval took approximately 400 days. Fiscal years 2013, 2014 and 2015, we have reduced this time by more than half each year with goals and the most recent goal being met in 2015.

And I'd like to stress these appropriate decisions with patient safety of paramount importance. One key change has been the interaction and engagement with sponsors and investigators.

I will also say that this has not been an easy transition and there has been a cost to staff engagement in this effort. And we continue to look for ways to make this progress sustainable long-term.

This webinar aims to help sustain these numbers by helping to educate sponsors and investigators and developers and innovators who are there able to start up their studies as quickly as possible, understanding FDA's expectations to getting these up and running.

And we can approve these studies safely in the U.S. (Unintelligible) messages that we want to accelerate getting devices to patients, who desperately need them and starting those studies in the U.S. is an important and critical first step.

Last, I'd like to mention that our division of neurological and physical meshing devices is one of the newest divisions in the Office of Device Evaluations at the Center for Devices and Radiological Health.

The office is the primary point of the device evaluation for medical device sponsors and investigators to engage the agency and we receive submissions for investigational studies or market approval in the U.S.

On the bright side called ODE, which there are seven divisions within this office, which is the last row and for which neural and physical medicine is one. Our division is growing.

And next month we are moving from three branches to five. Neurostimulation devices, neurology and psychiatry brands. The neurointerventional and neurosurgical devices branches and the physical medicine and rehabilitative devices branch.

And you will find no better teams of individuals positioned to safely move devices to move to market fastest. I'm a little biased. These five branches take on the lion's share of products dealing with neurological devices. And with

that, I would now like to turn to the non-clinical testing segment of this webinar with Molly and Dhanya.

Molly Ghosh: Thank you, Carlos. Good morning, everyone. My name is Molly Ghosh. I'm a toxicologist and lead reviewer in the Division of Neurological and Physical Medicine Devices at CDRH.

Today I'm going to talk about the biocompatibility assessment for neurological devices. Here is my presentation outline. First, I will provide an overview of biocompatibility assessment of medical devices in general.

And then I will discuss some special considerations for neurological devices. And, finally, I will provide an example of biocompatibility assessment for brain implants.

So there are two important considerations for non-clinical review of medical devices. One is performance. The question is, is a device going to perform as intended?

The other one is about safety. Is our final product going to be biocompatible? For today's talk, I will focus on the biocompatibility assessment. So what is biocompatibility?

Biocompatibility of a medical device referes to the ability of the device to receive the desired biological results without causing harm in the body. So it depends on the body's response to the device as well as device response to the physiological environment inside the human body.

So the next question is, you know, why do we ask for a biocompatibility assessment? We don't know always know everything in a final product. Also

it is important to know that CDRH regulates medical devices in its final, finished form.

It does not regulate the individual materials that are used to replicate the device. And you all know that biocompatibility assessment is a critical part of medical device safety evaluation. And we recommend the assessment to be done on the final stabilized applicable device.

And the reason is, you know, there could be different sources of toxicity from a medical device. It could be leachable chemicals or manufacturing residuals on the device. It could be potential degradation product or it could be some interaction between the leachable chemicals.

Also, the surface geometry, chemistry, and other properties can also adversely affect the biological response. So an assessment of potential biocompatibility risk from a device include assessing the effects of leachable chemicals from the device as well as the assessment of biological discourse to the device's properties and geometry of the device.

Also another consideration you need for the device is how biological response affects device performance. So ISO 10993 series of standards are widely followed for the biological evaluation of medical devices.

There are 20 parts to these standards. Some of the parts are really specific in testing guidance, while others are general. ISO 10993 part 1 provides guidance on biocompatibility assessment strategy.

It describes the device categorization and then recommends the assessment based on the category of the device. So I'd also like to mention here that in June of this year, we issued a guidance on the use of ISO 10993 part one.

And this is actually going to be implemented today. So I will strongly encourage you to review the standard, if you are planning any submission to FDA. Also I would like to mention about CDRH standard program.

And I provided a link to the guidance document on the recognition and use of this consistent standards. So as I mentioned earlier that ISO 10993 part one described device categorization.

So biocompatibility assessment, the devices are categorized based on nature of tissue contact and duration of tissue contact. So based on the nature of tissue contact, the devices are categorized as perfect contacting device, external communicating device, and implant device.

These standard duration of tissue contact, the devices are categorized as limited contact, prolonged contact, and permanent contact. The limited contacted devices are those that the contact is up to 24 hours.

Anything beyond 24 hours up to 30 is considered prolonged contacting device. And permanent contacting device has a contact duration longer than 30 days.

The device categorization actually facilitates the selection of the appropriate part compatibility endpoint for assessment. For example, you know, the biocompatibility assessment requirement for a permanent implant, like a deep breath stimulator, would be a lot more than a surface contacting electrode, which will be used for probably less than 24 hours.

So there is really no single endpoint that can predict the biocompatibility of a device. The biocompatibility risk from a device would be shot down like some

acute systemic toxicity or radiations to some long-term effects like chronic toxicity or genotoxicity.

So here is a list of the biocompatibility endpoints that you may need to consider depending on the category of the device. And as I mentioned earlier that the extent of the assessment depends on the device category.

Now I would like to mention also here that some of the endpoints like systemic toxicity and endpoints are, you know, or toxicity endpoints can be assessed through a chemical characterization risk assessment approach on the final finished device.

For some other endpoints, you may consider testing if the existing data could not be leveraged. So that's about from a basic information of the biocompatibility of medical devices in general.

Here I will provide some special consideration. You need to think of when you are assessing biocompatibility of neurological devices. So here are some examples of soft neurological devices.

This is no way a full list of diverse area products that we see. These are just some examples. And as we see that they are some base materials we just frequently use for this kind of products are listed in parenthesis after each of the product categories.

I would like to mention here that most of the time the biocompatibility issues that we see actually are not from the base material itself. It can come from the manufacturing residuals or some of the processing additives used in during the manufacturing of the device.

And that's the reason we recommend why the assessment should be conducted on the final phase device. For example, you all know (unintelligible) is a known neurotoxin.

And this is used in some polymer production. So if there is any small (unintelligible) in that device, you know, it might cause some toxicity. This is just an example.

So there are some special consideration for assessing the biocompatibility of neurological devices. As you all know, that the brain is protected by the blood vein barrier.

But when you're putting an implant in direct contact with neural tissue and function of the blood vein barrier. So there is a need for animal implantation testing in relevant neural tissue to assess the neurotoxic effect.

Also, we recommend that any devices in contact with neural tissue and CSF should be non-pyrogenic, meaning it should not cause any fever response. There are two sources of pyrogen.

One source is the chemicals from the device that can cause fever response. And that can be tested by the rabbit pyrogen method. Also there is another source called bacterial endotoxin, which can also produce fever response.

And that is assessed through the sterility assessment using that LAL testing. Also it should be noted that any implant or any devices in direct contact with CSF and neural tissue should have endotoxin limit of 2.15 endotoxin even if 25 or less.

As I mentioned earlier that, you know, chemical striation risk assessment approach could be used in lieu of testing for assessing some toxicity end points. But there are some limitations.

And this approach may not be relevant for assessing local tissue response. Also, you know, this chemical characterization risk assessment approach may only be used to assess the potential neurotoxicity of chemicals from neural implant, if the toxicological data on that chemicals are available from the study (unintelligible) these chemicals were administered through the clinically relevant route of exposure.

So here I'm going to provide an example on what other factors are endpoints to be considered, if you are assessing the biocompatibility of a permanent brain implant.

So the device category is considered a permanent implant with neural tissue and CSF and in direct contact with blood. So you need to assess the biocompatibility for ISO 10993 part one.

And I have researched some of the endpoints that need to be assessed in addition to this general biocompatibility endpoints, neural implantation study may also be considered to assess the neurotoxicity due to brain contact.

Also, as I mentioned earlier, the endotoxin limit should not go over 2.15 endotoxin unique (multiplied) for this type of devices. So also I would like to mention that currently there is really no standard protocol for a brain implantation study in the ISO 10093 standards.

There is a brain implantation study protocol being developed, which will be included as an annex in ISO 10993 part 6, which is the ISO standard for implantation.

But currently the standard, which is available does not have this protocol yet. Brain implantation study for neurotoxicity assessment. So if you are using a passive implant for your study, you might consider small animal models like rabbit models.

Other consideration could be separate test and control group, equal number of male and female animals in the study, and the inclusion of different time points to assess what acute and chronic responses.

Also, our study assessment parameters may include clinical observation neurobehavioral assessment, and histopathology to look at neurodegeneration, VOCs, and mild neuropathy for the neurotoxicity assessment.

You can also - you may also include some of the systemic toxicity assessment endpoints like body weight change, food consumption, chemical chemistry, the hematological parameters.

So this is just an example of if you were planning on doing a brain implant study. These are some of the points you may want to consider. So, lastly, I would like to mention also that, you know, if designed accordingly, your animal performance for a functional study can be used to address some biocompatibility endpoints.

Our next speaker, Dhanya Williams, will be talking about animal study, but here I'm just going to provide you an theoretical example. For example, you know, you are developing a new deep breathing stimulator system and you are

planning on doing large animal study with the active implant to probably evaluate some of the stimulation parameters.

What you can do also that - you can actually design this study to assess some of the biocompatibility endpoints like implantation, some of the systemic toxicity endpoints.

For example, you may consider including control groups like, you know, sham surgical control group to assess the effect of surgery on tissues, because, you know, surgery causes tissue trauma.

You might also - you may also consider including a control group with a passive implant to look at several - to look at the material mediated effects of the implant. Different time points may be included in your study design to look at acute and chronic responses.

Also, clinical observation behavioral assessment, histopathology, especially seems to look at neurodegeneration (unintelligible) could be included as a part of the neurotoxicity assessment.

Also, some of the systemic toxicity could be assessed through clinical chemistry, bodyweight change, pathology, etcetera. So that's - I would like to mention that if an animal study's designed properly to assess some of the endpoints, you may not need a separate biocompatibility study for implantation. So I will stop here and then hand it over to Dhanya. Thank you for your time.

Dhanya Williams: Hi, my name is Dhanya Williams and I am a biologist and a scientific reviewer in our division. This section of the webinar will focus on non-clinical animal studies.

So, first, what is the purpose of conducting an animal study? Animal studies are intended to demonstrate the device under study is sufficiently safe for early human experience.

For example, to support and IDE application or demonstrate device safety in support of a marketing application while incorporating modern animal care and use strategies. An animal study is warranted when there are performance evaluations or identified risks that cannot be addressed through bench of in vitro testing.

For example, the effects of technology or materials on brain function and neurotoxicity. Good laboratory practice as outlined in GLP regulations 21 CFR part 58, applies to non-clinical animal studies to ensure the quality and integrity of the safety data. GLP regulations also outline the basic elements that should be included in an animal study report for regulatory submission.

Non-GLP studies may be acceptable in some submissions, however, sponsors should provide adequate justification as to why GLP provisions were not met, how the study deviated from GLP, and why these deviations would not impact the study outcome.

For example, if an independent quality assurance individual is not utilized to periodically monitor various phases of the study, scientific justification should be provided to describe how the functions with the quality assurance unit were performed, in order to ensure the validity of the data and that the study was conducted in accordance with assigned study protocol. Also, please note that it's important to provide a full study report with your submission with a complete analysis of your data for review.

In this section of the webinar, we're going to be looking at some of the aspects that should be taken into consideration when designing a non-clinical animal study such as animal model selection, study size and duration and study endpoints.

It is important to plan a study in accordance with the device's indication for use and any planned clinical studies. This can really act as a road map for designing your animal study to address identified risks and to use procedures to conduct the study under clinically simulated conditions, when possible.

When selecting an animal model, it's important to provide scientific justification for the animal model that's used. An animal model should generally be accepted for the study of the device type.

This may be based on the utility of an animal model for a product class based on scientific evidence or literature. It is important to take into consideration the clinical relevance of implant or treatment site and understand the possible local and downstream responses.

Depending on the device, it may be recommended to use a simulated model to assess safety and/or performance. For example, the use of a simulated aneurysm for aneurysm devices or a simulated clot for neurothrombectomy devices.

There are some expected limitations to the use of animal models. For example, the tortuosity of neurovasculature of the animal model compared to humans or maximum defect sizes or size limitations due to the physical characteristics of the animal.

It is important to acknowledge or address these limitations. There's a great diversity in animal models that are used for neurological devices, ranging from rats and rabbits to sheep, swine and canines.

For example, in the past swine have been used for neurothrombectomy devices and canines and rabbits have been used as flow diverters.

When designing an animal study, study size and duration are important aspects to consider.

Studies should include the minimum number of animals necessary to generate valid and meaningful scientific data to demonstrate reasonable safety and performance.

It is important to include appropriate treatment and control animals for evaluation. This may consist of positive, negative, sham, predicate or reference device controls.

Study time points should be scientifically based on known tissue responses or risks from the use of your device. Studies should be designed to include animal cohorts to evaluate tissue responses over the course of the study based on the expected duration of clinical use.

For example, it might be necessary to evaluate both short-term and long-term responses for a permanent implant device. When selecting study size, it is also important to take into consideration the possibility of animal loss over the course of the study.

Finally, an important aspect of the study design is to include adequate endpoints to evaluate safety and performance based on the potential risks of the device.

For neurological devices, safety endpoints may include clinical observation such as neurological and behavioral assessments, hematology and blood chemistry, and upon termination of the study, gross necropsy and histopathology evaluations should be conducted.

It should be noted that there are various stains available for evaluation of tissue response or neurotoxicity. Also, as Dr. Ghosh mentioned earlier, certain elements of biocompatibility testing may be addressed in a well-designed animal safety and performance study.

Performance endpoints may include device condition following use and device specific functional endpoints. Additionally, labeling claims may need to be substantiated using the animal study.

When evaluating your device, methods to minimize bias should be considered. For example, blinding of the study, the use of multiple evaluators, and randomization.

It is important to include a thorough description of all procedures in your submission for our review, including administration of the anesthesia and medication, clinical, macroscopic or microscopic evaluations.

This segment of the webinar is designed to provide a general overview of non-clinical evaluation of biocompatibility and animal studies in support of an IDE or pre-market submission and we recommend that you contact our division using the pre-submission process to receive specific feedback regarding your

device. FDA will review proposed biocompatibility evaluation strategies and animal study rationale, design and protocols.

However, please note that data cannot be reviewed through the pre-submission process. Additional information regarding the use of the Q-sub process will be provided later in this webinar.

There are a number of resources available to provide information regarding non-clinical studies. As Molly mentioned earlier, the final biocompatibility guidance was published in June of 2016 and additional information regarding this guidance can be found in a related FDA webinar, which can be located through the CDRH learn link provided at the end of the slides.

The GLP requirements for non-clinical laboratory studies are outlined in 21 CFR part 58 and there is a recognized consensus standard website that provides a searchable database for standards recognized by the FDA and the extent of recognition.

Finally, a very useful resource is the FDA guidance document website, which provides a searchable database for both draft and final guidances including some neurological device specific guidances that may provide additional information regarding non-clinical testing and animal study recommendations for that specific device type.

So that concludes this section of the webinar and thank you very much. Our next set of presenters will be discussing the EFS program.

Erin Keegan: Good morning, everyone. My name is Erin Keegan. I'm a biomedical engineer and lead reviewer in the division. I'm also one of the early feasibility study representatives for the division.

So we're actually going to switch gears from non-clinical and we're going to talk about clinical testing. And Devjani and I will be discussing our favorite kind of clinical testing, which are early feasibility studies, which is a kind of IDE study.

So first I'm going to go through the definition of an early feasibility study and how it can potentially benefit you as a sponsor or investigator. Then I'll go through the stages of an EFS pathway to IDE and hit on some of the key submission milestones.

Then I'll start going through some of the key EFS principles and some examples for our division. And at this point I'll hand it over to Devjani to finish up key principles, go through some tips and talk to you about initiating your EFS.

So an EFS is a kind of investigational device exemption as Carlos mentioned earlier. So it allows you to collect clinical data to support device safety and effectiveness.

So an early feasibility study is a standard IDE, except it generally includes a small number of subjects, the device is generally early in development, so iterations are expected, and there may be limited non-clinical data and enhanced clinical mitigations may be required.

So it's important to note that EFS is an informal designation. And so you don't apply to be in the EFS program. If you have a very novel device and you want to get clinical data on a U.S. patient, then we will work with you as part of the early feasibility study program.

So how can an early feasibility study benefit you? So it permits a more efficient pathway to U.S. commercialization, because FDA feedback early on in your development may improve your development strategy and reduce unnecessary testing.

Also data collected in the U.S. patient population as maybe opposed to an OUS patient population may be easier to leverage to support later studies or marketing applications.

The EFS study itself also enables collect of high quality clinical data. And most of the time this will be the first time that the device is put into a human patient.

And so with this data you can optimize your device design or operator technique. You can refine the intended use population or non-clinical testing plan and it can also help you develop subsequent clinical study protocols.

So now I'm going to go through the stages of an EFS pathway to IDE. And these are all just recommended stages, but I'll start with we recommend that you reach out to Devjani and I informally.
This can be a phone call. And we're here, we will talk about your device. We won't be reviewing anything technical. That comes later, but we'll go through the EFS program, help you kind of organize your initial submission.

The next stage, again, this is listed optional, but they really are all optional, is to do an informational meeting pre-submission, which is a type of pre-submission.

And you can actually find more information about this in the Q-sub guidance. But these are essentially just a low pressure show and tell situation. You won't

receive any feedback from the agency, but it allows you to familiarize the review division with your device and clinical indication.

So then next you could submit your initial pre-submission. And this is actually outlined, the suggested content is outlined in the early feasibility study guidance.

And then I really want to highlight stage four, because the EFS process is highly interactive and collaborative. And so it's quite possible that you'll be submitting additional pre-submissions as you and the review team work through some of the non-clinical testing requirements and even the study design of the clinical protocol.

And then finally you submit your early feasibility study IDE just like any traditional IDE. And we have 30 days to review your study. So now I'm going to go through some of the key principles of EFS as we pulled from the guidance document.

Though I highly encourage you to actually read through the guidance document. You'll find a lot more information there and I'll go through some examples that may be relevant to our device space.

So the first principle is called Just in Time Testing. And so this came about from the concern or I guess motivation that comprehensive testing on really early phase devices may add significant costs without return.

Because you could be changing your device a month into your clinical trial based on feedback you've been receiving. And so we really want to stress doing the right testing at the right time.

And this should not take the place of informative non-clinical testing. And these will be worked out in those additional pre-submission processes between the review division and the sponsor.

So some examples could be deferring long-term durability testing given the criticality of short-term benefits for devices such as glioblastoma, spinal cord injury or severe psychiatric disorders this may be appropriate.

You could also limit the use of your device to a controlled setting such as a hospital or clinic instead of allowing the patient to take the device home in an early feasibility.

This could change testing strategy for electromagnetic compatibility for certain electronic based assistive devices. You could also use a small - for a small number of devices you may rely on single lot ethylene oxide sterilizations versus the full sterility validation.

So this may be applicable for a novel spinal cord stimulation lead.

The next principle I'll go through is the idea of using enhanced risk mitigation strategies in your clinical protocol. And so the concern here is that an EFS may carry greater unknown risks as compared to traditional feasibility and pivotal studies.

Because these are just such new devices and we don't have as much information to evaluate the risk assessment up front. And so how we handle this is build in clinical monitoring right into the protocol.

This could also include more frequent or detailed safety reporting to the FDA than you would see in a traditional IDE. And importantly the informed

consent should highlight the greater unforeseeable risk and the natures of these studies.

Because in the end the patients need to understand that this an early feasibility. So some examples could be if you have a stimulation, a stimulation device and you may be expecting some adverse events.

The ability to titrate the therapy or turn the device off and revert to standard of care could be used. If you have a novel endovascular stroke intervention or just a novel surgical procedure, you could consider selecting expert surgical sites so that there's control in that aspect.

Finally, if you have completed necessary biocompatibility and sterility, but you're still unsure about maybe the procedure or some aspect of the design and you want to monitor for infection, you could build that right into the protocol by having monitoring of the implantation site and the body temperature. So at this point I'm going to turn it over to Devjani to finish up the EFS topic.

Devjani Saha: Good morning, everyone. As Erin has mentioned, I'm just going to finish up the remaining EFS slide. So one of the pillars of EFS is the ability to leverage data from non-traditional formats such as literature or testing from marketed products or earlier prototypes that you may have.

It is important to understand that if you are considering leveraging data, you should provide a detailed discussion of the differences between the leveraged data and your proposed device.

These are differences in the materials, the device design as well as the manufacturing process. You should also include a strong leveraging rationale,

which discusses why, despite these differences, the data can still be used to support the safety and effectiveness of your device.

Some examples of leveraged data that we have seen in our division is leveraging of biocompatibility endpoints from functional animal studies that was discussed earlier in the biocompatibility section by Dr. Molly Ghosh.

Data can also be leveraged from published literature, so for example, with adequate justification, it may be feasible to leverage published spinal cord stimulation parameters to support stimulation parameters for a novel peripheral nerve stimulation.

So another key EFS principle is Timely Device and Clinical Protocol Changes. So devices under EFS may be early in development. And it's expected that the design of the device may change throughout the course of the study.

This highlights the need for timely device and clinical protocol changes. Changes to the device or clinical protocol may be accomplished through two different approaches, the first being contingent approval.

With this approach, device changes that you are anticipating during the study can be executed without necessarily additional FDA action, if the proposed changes, the supporting test plans, and the acceptance criteria were agreed upon in the IDE or IDE supplement.

There's also a broader implementation of the five day notice in EFS IDEs. So traditionally five day notices allowed for changes in the device design that were not significant as long as it did not affect the safety of the subject.

It also could not affect the validity of the data or the scientific soundness of the trials. These changes were allowed to be made prior to FDA approval, but the sponsor would need to inform the agency within five days of actually implementing the change.

In EFS, the five day notice is a bit broader, since EFS studies are associated with a small number of subjects and don't necessarily aim for statistical significance.

So, for example, the sponsor may be able to change the effectiveness endpoint to an EFS study as long as these changes don't affect the safety of the study. We've also seen 5 day notices which include minor changes to device design such as ergonomic modifications.

In terms of contingency approval, we haven't seen many of these in our division. But some hypothetical scenarios may include the ability to adjust simulation parameters and possibly interchange prosthetic device components without FDA approval, if the proposed changes have been agreed to during the review of the IDE or IDE supplement.

So for the next several slides, I'll be presenting some tips that we often give to new EFS sponsors. So if you're making device modifications, we highly recommend that you record the device modification along with the rationale for why the modification was made.

You should also record the testing that was completed with each device iteration. And you should keep samples of previous generations for leveraging in future submissions.

So, for example, you may be able to leverage some biocompatibility endpoints, if your previous generation had identical materials and similar manufacturing processes.

If you would like to use test results that were not obtained per standard FDA recommendation, we strongly suggest that you provide an explanation for why the data is sufficient.

So, for example, if your animal study deviates from GLP requirements, you should tabulate each part of the regulation, list how the study deviates, and describe how you will still be able to ensure the integrity of the data and minimize bias.

The next tip deals with the use of short-term animal studies to support EFS initiation of a device that's intended for long-term use. So if you're planning to do this, we strongly recommend that you provide supporting evidence that short-term results are predictive of long-term safety.

You should also consider applying additional clinical mitigation strategies such as longer term follow up. And you can also think about conducting additional non-clinical testing such as mechanical integrity testing under exaggerated use conditions and perhaps also support your submission with computational modeling to support the long-term safety of your device.

Please note that additional long-term animal data may be needed to support a larger clinical study. So when do you know that you're ready for an EFS? Well, it’s generally when you can describe why additional non-clinical testing will not be informative and therefore a human study is necessary.

You can also justify how any leverage information supports your clinical trial and you can identify the potential risk and how they will be adequately mitigated.

We recommend that you communicate these points to us using a device evaluation strategy as described in the EFS guidance. And the link is provided in the slide here.

We're often asked by sponsors, "When is a good time to talk to the FDA about EFS?" Well, it's typically after you've established your general device design, you have an idea of your intended use, and what information you would like to gather from the EFS.

And we strongly recommend, that you come talk to us before conducting expensive, and time consuming, non-clinical testing. We also recommend that you reach out to the division EFS representatives, which are Erin and myself to informally discuss the submission strategy.

Our contact information can be found at the end of the presentation. Thank you for your time. And now I'll hand the mic over to Tim Marjenin, who will present an FDA engagement and the pre-submission process.

Tim Marjenin: Thank you, Devjani. So, my name is Tim Marjenin. I am the chief of the Neurostimulation Devices Branch in the division and I'm going to be covering a few key aspects of the Q-sub guidance.

The guidance covers multiple types of interactions. Today we will focus primarily on pre-submissions, with also a little bit at the very end of my presentation, about risk determinations.

So, one of the big things that always comes up with regards to pre-submissions, is the timeframe for review. And per the guidance, we do try to hold a meeting, if you request one, within seventy-five to ninety days when we acknowledge receipt.

So we will provide feedback, about 3 days in advance, if you request a meeting. You should, generally, plan to meet with us or receive that written feedback within about that time frame due to the work load considerations of review staff.

So, please budget your time accordingly as you're planning out how long you anticipate various steps in the process to take.

Why engage as early as you can? Well, pre-submissions allow for central issue to be identified earlier and we can work with, work through them with you as appropriate. Particularly, if you might have some type of novel technology or some sort of novel testing.

You can always submit a supplement to get additional feedback if additional things come up. Or, if you revised something and you want our feedback on revisions.

One of the common issues that we see with regards to pre-submissions, it's actually a fairly common issue across the spectrum of submission types, is e-copy.

You really need to make sure that you comply with the e-copy guidance, because, if you don't, your submission will not be officially logged in, the review clock doesn't start, and nothing else happens.

I won't even know that it exists. And so there is an email address here. You can direct questions about the e-copy program to that email address.

As far as submission contents are concerned, it's pretty basic and fairly general. Cover letter, background information, necessary information about device description, the types of protocols that you're running, whether it be bench or animal clinical study protocols, if there are any specific questions related to that background information.

One of the common issues that we see with regards to this is you - not enough information is provided up front. So, a few years ago we did an analysis of investigational devices exemption letters and we found that the area generating the most questions was actually, device description. What the device is and does, instructions for use, the hazard analysis.

And this is something that we see across the other submission types. If we don't have enough information to understand the device, we end up asking a lot of questions. And, providing complete responses to those questions takes your time, and that extends the overall length of the review.

So it's important to remember, that you as the applicant, know the most about your technology, and not the FDA. The more that you can explain the thought process when you submit the pre-submission upfront, the more we can focus on the substance and give you better feedback.

It's also helpful to understand the existing landscape as you're doing this. So, please search for and review applicable guidance documents and standards, if there are any, such as biocompatibility, which you heard about earlier. As well as other things, like software, which applies to a lot of devices that come through our division.

Make sure you explain the relationship of what you are proposing, compared to what's been done in the past. As far as background information, it really is okay to err on the sides including more of what you think might be needed. Just make sure that it's organized and easy to follow.

And if you intend to cite literature, articles, please provide copies in the submission. There is such a thing as providing too much information. It's fairly rare. We don't need to see circuit diagrams for your devices.

We don't need to see lines of software code. We don't need to see a copy of the entire grant that you may have submitted to NIH.

It's good to avoid assumptions. Unless there is an applicable guidance document, an applicable standard or another regulatory precedent that you can cite, it's a good idea to identify the most appropriate approach for your needs, and to justify it.

For example, not every animal study needs to use a non-human primate model. Some other type of model and protocol might be better suited to your particular situation. We also see some issues when it comes to specific questions. For example, not providing your own proposal for us to review.

It's not really a great question to say, "What animal should we use?" Or, "How large should the sample size be," if you're talking about a clinical protocol. We also get questions every now and then about wanting us to review data.

"Does FDA have any comments on the non-clinical test results?" That's something that's left for the review of the actual marketing submission or an

IDE, if that's the case. When it comes to specific questions, they should build on the background information that you've provided.

So, rather than saying, "What animal model should we use," you obviously proposed one in the submission. "What concerns do you have with our proposed animal model?" It's helpful if you've said "Here are some of the approaches that we've considered. Here is why we think ours is the most appropriate for our situation."

Another example of a good question: "Are the proposed sample size calculations method end related elements of the statistical analysis plan appropriate for the proposed clinical study?" Again, getting us to comment on the approach that you have proposed.

Let's finish up with a quick slide related to significant risk, non-significant risk and basic physiological research, with a focus on when an IDE is not required.

An IDE is not required in several different circumstances. For example, if there are exempt studies, for the IDE regulations, such as studies of approved devices that are used in accordance with your labeling.

Also, certain diagnostic device studies. An IDE is also not required for a basic physiological research, which is not for the purpose of evaluating safety or effectiveness of the device.

We also don't need an IDE for practice of medicine when you're talking about care of a specific patient with an approved device. And finally, we don't need an IDE for non-significate risk studies. The IRB can and should be making the first cut as to whether an IDE is required.

However, if you still have questions about that, there is another type of Q-sub, referred to as a risk determination request, which is outlined in the guidance document.

You can send that in to us and we will evaluate it, and the outcome will be a letter saying either that you're a significant risk, you need an IDE. Non-significant risk, you don't need an IDE, or its basic physiological research, in which case you would also not need an IDE.

That concludes my section of the presentation. I'm now going to turn the microphone back over to Dr. Pena, who will close out with some remarks.

Dr. Pena: Thanks, Tim. So, a few closing thoughts. Our job at FDA, is to ensure the safety, effectiveness and security of a wide variety of medical products. Including medical devices and neurological devices.

Neuro-technologies represent the merging technology area that we very much want to support, and make our nugatory landscape, as transparent as possible.

Along these lines, we encourage industries, sponsors, developers, innovators, to consult earlier with the agency, which offers FDA staff the opportunity to clarify the data needed to bring safe and effective products to market in the fastest way possible.

And most importantly, the faster we are able to evaluate products that are safe and effective, potentially, the faster patients (unintelligible) and get the products they desperately need.

And I would like to thank the staff, in the planning, the execution, and the presentation of this webinar for FDA that is for this session. On the next few slides, we provide a primary point of contact for the Center Device Division and Consumer Education as well as additional resources, should you have questions.

That is a very good place to start. And, with that, I would like to close the presentation portion of this webinar. We are going to take approximately a one minute break and then we will open the session to questions and answers. Thank you.

Coordinator: Momentarily, we will be beginning the formal question and answers session of the call. At that time, if you'd like to ask a question, please press Star then 1, and clearly record your first and last name. If you'd like to withdraw your question, you may press Star then 2.

Again, to ask a question, please press Star then 1, unmute your line and clearly record your first and last name. There will be a brief moment between each question. Thank you, we will be beginning momentarily.

We would now like to begin the question and answer session. Again, to ask a question, please press Star then 1 and clearly record your first and last name. Please try to limit it to one question, per person. If you have additional questions, you may re-queue for additional questions. One moment for the first question please.

Carlos Pena: Me again. I might take the prerogative as this (unintelligible) ask a couple of questions to our staff. One question that we often get, that I've often received in conferences, and in correspondence, is sort of like, you never ask 1 question, you ask 3 questions.

"Is it, is it ever too early to contact FDA? What is the best way to engage FDA? And, who should I contact?" And so, I'd like for Tim, to give that response, because I think they're aligned well with those questions going well with the best practices to get us started.

Tim Marjenin: Is it ever too early? Well, not really, unless you just have nothing done. So, even if you are fairly early on in the process, and this is something that I didn't cover as part of my slides, but the aspect of the Q-sub program is, and this was alluded to, in the EFS discussion was, the idea of informational meetings.

And those are a great way too for sponsors to familiarize us, FDA, with your product, with where you are, where you're going, what you have, what you intend to do. Those are things that, that, even though the timeline outlined in the guidance is 90 days, it's something where we can generally have a meeting a bit quicker.

Because there really is nothing for us to review at that point. It really is just kind of a show and tell. And if we have some off the cuff questions, we may raise those during the meeting. And those can be, those can be a good intro to FDA and which can certainly be followed up with one or more pre-submissions for specific clinical and non-clinical protocols, and things like that.

The best way to engage is through things like that. Taking advantage of the informational meeting, pre-subs, things along those lines. Coming in, trying to come in just so you can understand as many of the expectations as you can before you get to far down in the process, and you run all these tests, only to

learn there at the end that, well, maybe that wasn't actually what we were looking for.

The whole idea is to try and make the process as efficient as possible and to make sure that everybody understands the expectations as you're going through the process. And, the pre-submission process is a great way to do that.

And then as far as who to talk to, well, if you happen to see somebody at a conference, and you know that they are FDA, you can say hi. We're friendly people. If you have specific questions, and we're not in a conference situation - when you have a contact, here at FDA, let's say it's somebody in this division, you can send us - you can send us a question.

That individual may or may not be the right person to ask. If so, then they will try and answer your question to the best of their abilities, as quickly as they are able to, considering their other work. Or, if they are not the right person to talk to, they can certainly take it over to, who would be the right person.

And, if you don't really have a good point of contact, I will throw my name out there, as one of the three branch chiefs. Branch chiefs are always a good point of contact to, to start with if you have a general sense for where your product would fall.

Carlos Pena: One additional question that I think with studies is - you know, one question that we get is, "I'm somewhat sure that I think I can go to an EFS study, but I'm not quite sure, if I'm really ready to submit. How do I just talk through, whether I have an EFS study or something other?" Maybe Devjani and Erin, you can respond to that question.

Erin Keegan: So, I think that's a pretty common question, and the best thing to do is just to reach out to Devjani and I. You can email us and we typically will set up some phone calls.

We do those frequently, actually. And, we can discuss your device and what you plan, what you want out of this study, actually, is an important question. So if you want to do a statistically, significant, large study, maybe EFS is not right for you.

But, yes, it's pretty informal. We talked through some principles and we help you plan your submission strategy. I don't know if Devjani has anything to add?

Devjani Saha: So, one other thing, is that for EFS, we typically, you know, we try to see where the number of subjects are, so there are typically smaller studies. But there have definitely been incenses where, you know, you have a smaller study, but it may not necessarily be suitable for EFS because there is something very similar that you have already, you've already submitted as an IDE.

So, you don't need to go through the entire list mitigation because that is already kind of with us and we have that on file and it might be easier just for you to do a supplement. So, there are certain nuances, and we highly recommend that you reach out to Erin and I to discuss those informally.

Carlos Pena: Without any further questions, I'd like to thank the presenters, the meeting organizers, and the folks, the many staff that were involved in the execution of this webinar. The information is posted online. Folks can take a look and if they have questions, following this session, be happy to address questions as needed.

And, we hope to share with you more about upcoming regulatory webinars in the neurological and physical medicine devices base, coming up next year in 2017. As it also relates in support of the White House brain emissions. And with that I'm going to turn it back to Irene.

Irene Aihie: Thank you. This is Irene, I hear. We appreciate your participation and thoughtful questions. Today's presentation and transcript will be made available on the CDRH Learn webpage at www.fda.gov/training/cdrhlearn by Thursday, September 22nd.

If you have additional questions about today's webinar, please use the contact information provided at the end of the slide presentation. And, as always, we do appreciate your feedback. Again, thank you for participating and this concludes today's webinar.

Coordinator: This concludes todays call. You may disconnect at this time.

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