

**FDA Webinar: Regulatory Overview for Developers and Sponsors of Neurological Devices:
An Introduction to Humanitarian Device Exemptions (HDEs)
Moderator: Irene Aihie
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Coordinator: Welcome and thank you for standing by. All lines are in a listen only mode until the question and answer session. The question and answer session will be at the end of the presentation and only from the phones. At that time, you may press star 1 and record your name. Today's conference is being recorded. If you have any objections, you may disconnect at this time. I would now like to turn today's meeting over to Irene Aihie. Thank you. You may begin.

Irene Aihie: Hello and 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 efforts 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, an overview of the HDE regulatory pathway, information about humanitarian use devices, also known as HUD, including information about use and the pediatric population, health systems for completing an HDE application and we'll be discussing concerns of HDE manufacturing.

Dr. Carlos Pena, Director of the Division of Neurological and Physical Medicine Devices, in the Office of Device Evaluation here in CDRH, will start today's presentation. He will be joined by members of the division. Following the presentation, we will open the lines for your questions related to information provided during the presentation. Additionally, there are other

subject matter experts here, to join the team, to assist with the Q&A portion of our webinar. Now I give you Carlos.

Dr. Carlos Pena: Good afternoon. Welcome to the FDA seminar on a regulatory overview for developers and sponsors of neurological devices. I have an agenda. We will be discussing the following - an introduction to humanitarian device exemptions, followed by a program overview, HDE basics and pediatric considerations; similarities and differences between PMAs and HDEs; HDE manufacturing concerns, a risk/benefit analysis and a few closing remarks. And then as Irene mentioned, the Q&A session will follow.

This session is sponsored in part, by staff across the agency. And I'm very grateful for all the staff who have contributed to this event. At CDRH, our vision is that patients in the US, have access to high quality safe and effective medical devices of public health importance, first in the world. For some background, a medical device is defined as an instrument intended for use in the diagnosis or cure, mitigation, treatment of and prevention of a disease or intended to affect the structure or in function of the human body. And does not achieve any of its primary intended purposes through chemical action.

And we can classify a device as a medical device even in the absence of claims, when a device impacts the structure and function of the human body. So you're probably saying, Carlos this is quite a lot to remember. But as a take home message, if the device typically diagnoses, prevents or treats a disease, it may very well be a medical device.

Now we have been engaged in this technology sector for some time and this is a favorite slide of mine. Here I show you an array of products with neurological indications, beginning with a neuro-diagnostics device, deep

brain stimulation devices to surgical kits, catheter systems, stent-assisted coils and neurological microcatheters during surgery.

Many of these products treat a disease or condition and the majority of products will authorize for marketing, under the humanitarian device exemption or HDE pathway. 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 or in this case of HDEs, probable benefit of the device. And you'll learn a little bit more about different aspects of this regulatory pathway.

I would also like to note, as an intro, that medical devices can be categorized into a number of types - including four which are listed here. The Class 2 and Class 3 descriptions are high risk classifications that can be linked to regulatory submission pathways. For example, we receive several dozen PMAs each year. These submissions are the highest risk and require clinical data. These are class 3. Another pathway is 510(k) submission. And we receive several thousands each year. And 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 clinical data. These are class 2.

And a third regulatory pathway is a de novo submission process which includes devices that aren't comparable to anything on the market and present a lower risk than other types of devices. Typically, once we've granted a de novo, that particular product becomes the predicate to subsequent products, which can then move along the 510(k) pathway.

And the focus of this presentation, HDEs, are medical devices that are intended for diseases or conditions that affect small, rare populations. So as I've just noted, there are a number of regulatory pathways to bring a device to

market. And for a more recent paper that FDA published last year, Neuron, we show several of those pathways, such as the pre-market approval pathway, the pre-market notification or 510(k) pathway. And at the lower half of the slide, the HDE pathway, which Katie will be discussing shortly.

We received a number of HDEs across the division. And here I show one last slide on the organization of our division in the pre-market side review, and a distribution of products across each of the branches as we now delve deeper into the HDE process. And I turn to Ms. Katie Chowdhury, from our HDE staff.

Katie Choudhury: Thank you Carlos. My name is Katie Chowdhury and I am a biomedical engineer in the Office of Orphan Products Development. I'm going to provide an overview of the Humanitarian Use Devices or HUD programs. Per the definition outlined in Title 21 of the Code of Federal Regulations or CFR, under Section 814-3N, a humanitarian use device is a medical device intended to benefit patients in treatment or diagnosis of a disease or condition, that affects or is manifested in not more than 8000 individuals per year in the United States.

In 1990 Congress established the HUD designation in HDE marketing pathway program. This program was created to encourage the development of devices for disease - rare diseases or conditions. Congress recognized the small market would create an economic disincentive for device development for rare diseases. Traditionally, in order for a device to enter the US market, there has to be a reasonable assurance that the device is safe and effective. Under the HUD HDE pathway, the sponsor is exempt from having to demonstrate device effectiveness and needs to demonstrate the device is safe and provides a probable benefit to the patient.

Therefore, the HUD HDE program is an alternative pathway for devices intended for rare diseases or conditions, to enter the US market. There is a two step process if the sponsor wishes to get their device commercialized in the United States, through the HUD HDE marketing pathway. First, a sponsor must submit a HUD designation request, and receive approval from the Office of Orphan Products Development. Second, once the HUD designation is granted, the sponsor submits their HDE marketing application to either the Center for Devices and Radiological Health or sometimes, if the device is a biologic, to the Center for Biologic Evaluation and Research.

We have provided the Web site link on this slide if you wish to gather additional information on how to get a HUD to market. In order to be considered for an HDE, a sponsor must first submit a request and receive a HUD designation from the Office of Orphan Product Development, as previously described. The submission must include one paper copy, the original, and one eCopy. The request should contain a cover letter. This should request that OOPD consider the device for a HUD designation for a rare disease or condition or an orphan subset of a disease or condition.

The HUD request should describe the disease or condition that the device intends to treat or diagnose. You should also provide a proposed population estimate. This is a calculation of the number of patients affected or manifested with a disease or condition in the United States per year. The request should tell us how the device - about the device and how it is used. This should include a written description of the device, including engineering diagrams, as well as a scientific rationale supporting use of the device.

Please include all relevant pre-clinical, clinical and/or proof of principal data pertaining to the device. And finally, the request should include supporting documentation with applicable references, demonstrating that the device is

designed to treat or diagnose a condition or disease or orphan subset that occurs in not more than 8000 individuals per year in the United States.

We have a guidance for HUD designation that can be located using the following link, for more information on what to include in your application. OOPD reviews each request in a specific consistent manner. First, we evaluate the disease or condition that device is intended to treat or diagnose, based upon the device's functionality. Second, we consider the target population that may benefit from the use of the device.

Please note that we may broaden the requested designation if we determine that the device may be used to treat or diagnose people, more people with that disease or condition. The caveat here is that the entire population with the disease or condition, must not be more than 8000 individuals per year. If the target population is over 8000, a sponsor may still obtain a HUD designation if they can explain why the population is an orphan subset.

OOPD conducts the HUD designation request within 45 calendar days, and then issues the sponsor a decision letter. OOPD may approve, disapprove or request additional information during our review. Approval means that the device is designated for the disease or condition that occurs in not more than 8000 patients per year. Please be aware that disease or condition that is approved and receives the HUD designation may not be the one requested by the sponsor, if the device may treat a broader or more defined disease or condition.

After an application receives HUD approval, they have the ability to submit an HDE to CDRH receiver. We disapprove a designation if we determine that the population exceeds 8000 patients per year. For purposes of HUD requests, the pediatric population is defined as those younger than 22 years of age. This

includes the patient's 21st year of life. Generally, OOPD will designate the entire population, both pediatric and adult, if the population estimate of the disease or condition affects or is manifested in not more than 8000 patients per year, in the United States.

However, if the overall population exceeds 8000 patients per year, a sponsor may pursue a pediatric population if that is not more than 8000. That concludes my talk and I am now going to pass it onto Anupama.

Dr. Anupama Govindarajan: Good afternoon. I am Anupama Govindarajan. I am a lead reviewer in the Division of Neurological and Physical Medicine Devices. And today I would like to discuss with you the basics of HUDs, HDEs and their pediatric considerations. The diagnosis of a rare disease or condition can be a devastating consequence for the patient and their family. Only a portion of 7000 known rare diseases have approved treatments in the United States.

By definition, rare diseases or conditions occur in a small number of patients. As a result, it has been difficult to gather enough clinical evidence that the FDA standard of reasonable safety and assurance. As a result, it was uncommon for medical devices for rare diseases or conditions, to be legally marketed in the United States. HUD - an HUD is a medical device intended to benefit patients in the treatment or diagnosis of a disease or a condition that affects or is manifested in not more than 8000 individuals in the United States, per year.

HDE - Section 520M of the Federal Food & Drug Cosmetic Act of, the FD&C Act, an HDE is a marketing application for a HUD. An HDE is exempt from effectiveness requirements of Sections 514 and 515 of the FD&C Act and it's subject to certain process for use restrictions. There are two steps to get an

HDE to market. Step one, first the applicants must obtain a HUD designation from the FDA's Office of Orphan Products, referred to as OOPD.

Step two, after the device is designated as a HUD, the applicant then submits the HDE application to the proper FDA review center. Either the Center for Devices and Radiological Health, CDRH, or the Center for Biologic Evaluation and Research, CBER, depending on which center regulates the device. A device is eligible for review in an HDE application if it meets two criteria. First, OOPD must designate the device as a HUD. And second, they cannot be a legally marketed device for the same disease or condition granted under another regulatory pathway that is pre-market notification, pre-market approval or the de novo path.

The approval threshold for an HDE, is based on two factors - the first is a reasonable assurance of safety. Note that the law that created the HDE program, did not change the regulatory standard for safety. In other words, the safety button is the same for both (PME) and HDE devices. Reasonable assurance of safety consists of not posing an unreasonable risk of illness or injury to the patient. The second factor is specifically what was addressed in the law that created the HDE program.

Specifically, the law exempted HDE devices from demonstrating a reasonable assurance of effectiveness and instead, requires demonstration of probable benefit. This difference in determination of effectiveness is the key difference between the (PME) and HDE application. The basis to approve an HDE is the demonstration that the use of the device or its probable benefit outweighs the risk of injury or illness from its use. This also takes into account considerations whether other available options are available as well as their respective benefits and risks.

What these other devices are already marketed for the similar indication. The FDA will only consider HDE applications if there is no comparable device available to treat or diagnose the disease or condition, unless the comparable device is also approved under an HDE or is still in the testing phase under an investigational device exception or the IDE. Comparable device does not necessarily mean identical.

If the indications for use, technological characteristics and patient population are all the same, FDA may consider the device comparable. The FDA has issued a final rule requiring sponsors of medical device applications to submit data on pediatric patients as a condition of approval.

We will now discuss the content of an HDE application. Every HDE application should include the following - a copy or reference to the approved HUD designation letter.

The applicant should provide a written explanation of why the device is not otherwise available, and a statement that no comparable device is legally marketed. The application should include descriptive information about the device, such as a device description, including discussion of all device components and accessories, and how they work; design drawings and specifications, and a listing of the materials of use.

The application should include a statement of the proposed indications for use. This should be consistent with the HUD designated disease or condition referenced in OOPD's HUD designation letter. The bulk of the submission will consist of the valid scientific evidence to support the safety and probable benefit of the device. This evidence may include a variety of information and data sources, such as bench testing, animal testing and all clinical evidence.

As a conclusion summary of this valid scientific evidence we ask them to explain why the probable benefit outweighs the risk of use of the device.

The HDE application should also contain manufacturing and submission. Note that the device must comply with the quality system regulation reference in 21 CFR Part 820.

The amount to be charged for the device as well as a statement indicating that the cost of the device does not exceed the cost of the device in such development for application and distribution. Sponsors can also apply to profit off the devices if the device is intended to treat pediatric patients or if the device occurs in such low numbers that its development would be impractical or impossible.

The application should include the physician labeling and if applicable, the patient labeling. The labeling for an HDE must contain a statement that the device is a humanitarian use device and that though the device is authorized by federal law, the effectiveness of the device for the specific indication has not been demonstrated. The clinical evidence submitted in the HDE, should preferably include summaries, conclusions and results of all clinical experience or - of investigation. The information should include evidence that supports both the safety and the probable benefit.

We now discuss the possible clinical study limitations in HDE applications. The clinical evidence submitted in the HDE should preferably include summaries, conclusions and results of all clinical experience or investigations. The information should include evidence that supports both the safety and the probable benefit. FDA recognizes that there are limitations and challenges in the collection of relevant clinical evidence for an HDE device.

Because HDEs are limited to patient populations with a rare disease or condition, it's maybe challenging to find and recruit these patients into a clinical study. This may lead to smaller sample sizes in a perspective clinical study. And second, because there is no available comparable device for the same indication, these studies may lack an active control and/or randomization.

If you are designing a clinical trial for an HUD HDE device, we strongly encourage you to discuss the protocol with us, in a pre-submission, so we can help provide feedback on the most appropriate clinical study, considering the limited population and appropriate benefit and risk measure. Pediatric requirements for an HDE - in January 2014, the FDA finalized its guidance on pediatric information required from sponsors of medical devices, including HDE sponsors.

FDA defines pediatric populations as including neonates, that is from 0 to 28 days; infants, less than two years; children, 12 to 2 years of age; and adolescents, under 21 years of age. The Food & Drug Administration Safety and Innovation Act (unintelligible) Section 515a, calls for two pieces of information from each device applicant. A description of any pediatric subpopulations that suffer from the disease or condition that the device is intended to treat, diagnose or cure.

The caveat is that such information must be readily available and addition intended to prevent companies from needing to extensively seek out none of the (patient). Until the number of affected pediatric patients. A limitation of HDE approval is with the approved labeling, the device must clearly identify the device as an HUD, it must state that the effectiveness for that indication has not been demonstrated.

The labeling must identify the pediatric population if the HDE was approved for a pediatric specific-indication. I will now hand this talk over to (Kelly Ann), who will talk about PMAs and HDEs.

(Kelly Ann Watratich): Thanks Anu. Good afternoon. My name is (Kelly Ann Watratich). I'm a biomedical engineer and lead reviewer in the Division of Neurological and Physical Medicine Devices. If you've submitted a PMA to FDA in the past, then you may be familiar with some of the requirements and regulatory aspects that are also (unintelligible). However, there are significant differences in the HDE regulations and review process that should be highlighted and considered before submitting an HDE. We'll set them to (unintelligible) describing the similarities and differences.

On this slide is a table showing a general overview comparing and contrasting PMA and HDE review paradigms. Firstly, the indication for use in the HDE is limited by the indications for which a sponsor obtains a humanitarian use designation. The process previously described by Katie from the Office of Orphan Products Development. Secondly, the law exempts HDE devices from demonstrating a reasonable strength of effectiveness, and instead, requires demonstration of probable benefit.

This difference in determination of effectiveness is a key difference between applications for pre-market approval, PMAs and HDEs. The review timeframe also differs between HDE and PMA submissions, with HDE decisions determined typically within 75 days. The timeframe of a PMA depends on whether it requires a panel that can be between 180 to 320 days.

After approval, HDEs may only be used in facilities with IOB oversight. And unlike PMAs, HDEs may not be sold for profit, except for in certain circumstances. The next few slides we'll delve into a little more detail

between these similarities and differences. Slide 30 steps through these similarities. Both PMA and HDE submissions, undergo an initial administrative review within the first 30 days of receipt, known as the filing review. The filing of an HDE means that the FDA has made a threshold decision that the application is sufficiently complete to permit substantive review.

Both PMAs and HDES may be submitted for modular review. A modular PMA or HDE is a compilation of sections or modules submitted at different times, but together become a complete PMA application. The modules may be separated into specific topics, such as pre-clinical, clinical and manufacturing. FDA intends the modular review approach to provide a mechanism by which applicants may submit pre-clinical data and manufacturing information for review, while still collecting, compiling and analyzing the clinical data.

Therefore, a modular PMA is a compilation of sections that over time will complete an application. The modular approach also allow applicants to potentially resolve a deficiency noted by FDA earlier in the review process, than would occur with a traditional PMA application. Quality system regulations or QSR, apply to both PMAs and HDEs. However, we primarily focus on those manufacturing practices that the agency deems most relevant to the safety of the device.

After approval of both PMAs and HDEs, several documents are publicly posted, including a detailed summary of the data on which the approval or denial decision is based. However, the name of those summaries differ and reflect the level of data required for the submission type. The summary of safety and effectiveness data or the FSED, are posted for PMA approval. Summary of safety and probable benefit or SSPD, are posted after HDE

approval. Also after approval, both PMA and HDEs have some similar post market that requirements, such as potential completion of a post approval study, as well as submission of annual report.

HDE amendment supplements and reports, are generally subject to the same regulations as those for PMAs. Now that we've gone through some of the similarities, here are some key differences that make HDEs unique and are important for you to note before submitting an HDE. The first important step and difference between PMAs and HDEs, has been said a few times before, but you must demonstrate that the intended patient population of the device does not exceed 8000 in the US per year.

User fees for HDEs, are waived under the Medical Device User Fee and Modernization Act of 2002 and have been reauthorized and amended by the Medical Device User Fee amendment of 2007. As previously noted in the table describing the differences, HDEs are exempt from demonstrating effectiveness and should demonstrate probable benefit. In demonstrating probable benefit, the sponsor should consider including an explanation of why the probable benefit to health from the use of the device, outweighs the risk of injury or illness from its use, taking into account the probable risk and benefits of currently available devices or alternative forms of treatment.

(Vaccination) can be (supported) by clinical experiences or investigations whether adverse or supported, that are reasonably obtained and that are relevant to the assessment of the risks and probable benefit of the device. When an HDE is approved, the device is considered unclassified while a PMA applies the class 3 devices. And as long as the HUD is being studied for indications and its approved labeling, the HDE is not subject to IDE requirements because the - I'm sorry. Excuse me. The HUD is not subject to

IDE requirements because the HUD is a legally marketed device and can therefore be lawfully shipped without an IDE.

However, other clinical investigations require requirements that will apply including IRB approval and protection of human subjects, including informed consent and if applicable, additional safeguards for children. Once approved, HDEs also have several post market limitations that differ from PMAs. HDE devices require (IRB) approval before being used in a facility. As Anu previously mentioned as well, the HUD labeling and materials may include the phrase FDA approved, similar to PMAs.

Also similarly, HDE labeling and materials, must be truthful and not misleading. But it should also include a statement clarifying that effectiveness has not been demonstrated. HDEs may not be sold for profit, except in certain circumstances. An HUD is only eligible to be sold for profit, after receiving HDE approval if the device meets the following criteria. The device is intended for the treatment or diagnosis of a disease or condition that occurs in pediatric patients or in a pediatric sub population and such device is labeled of use in pediatric patients or in a pediatric subpopulation in which the disease or condition occurs.

Or the devices is intended for the treatment or diagnosis of a disease or condition that does not occur in pediatric patients or that occurs in pediatric patients, in such numbers that the development of the device or such patients, is impossible, highly impracticable or on faith. If an HDE approved device does not meet either of those eligibility criteria, the device cannot be bought for profit.

HDE applicants whose devices meet one of the eligibility criteria in which to sell their HUD for profit, should provide adequate supporting documentation

to FDA in an original HDE application, to demonstrate to FDA that the HUD meets those eligibility criteria. To continue with some additional differences between PMAs and HDEs, HDEs cannot be approved once a comparable device with the same indications for use, is marketed through a PMA or 510(k). In contrast, there may be multiple PMAs or 510(k)s approved or cleared for the same indications for use.

Compassionate use provisions may also be applied to HDE devices. Patients may have access to investigational devices that have not received FDA approval or clearance for patients for whom the treating physician believe the device may provide a benefit in treating and/or diagnosing the disease or condition. And if you happen to have an HDE, you can also transition this HDE into your PMA. A PMA may be submitted if you're seeking to make a profit from an HDE device or if you're seeking a different indication that might be assessed in more than 8000 individuals per year.

Please note that when submitting a PMA for an HDE device, for a different indication for use than previously approved in an HDE, the effectiveness level will shift to the PMA review paradigm, requiring you to provide information that demonstrates reasonable assurance of effectiveness. This may include additional bench, non-clinical and clinical data. And as I previously described, you may collect safety and effectiveness data to support a PMA or an HDE approved indication, without an IDE.

While the work is done to collect such safety and effectiveness data to support a PMA, constitutes a clinical investigation, FDA considers the sub data exempt from the requirement of an IDE, as long as the (HUD) is used in accordance with its approved indications. This concludes our discussion on the similarities and differences between PMAs and HDEs. I'll now pass the presentation onto Matthew Krueger.

Matthew Krueger: Good afternoon. I'm Matthew Krueger and I'm the Branch Chief for Physical Medicine, Orthopedic Neurology and Dental Devices in the Division of Manufacturing and Quality in CDRH's Office of Compliance. We are responsible and tasked for reviewing the manufacturing information both for PMA submissions and for HDE submissions to the agency. We'll talk a little bit today about manufacturing related submissions. That includes original and modular HDE submissions; how preapproval inspections fit into that briefly; and then we'll talk about some other submissions to the agency, including site change supplements and 30 day notices.

As discussed and mentioned by (Kelly Ann), there are many similarities between PMA submissions and there are also some differences between HDEs and PMA submissions. So we'll talk a little bit about those. Some of the similarities relate to the information that you need to submit. So for both PMAs and HDEs, manufacturing information is required and the same information is required in each of those submissions. There's not a specific HDE guidance, but there is a PMA guidance relating to the required information, manufacturing information to be submitted in a PMA supplement and we'll refer to that. There's a link later on in the presentation to that guidance.

Manufacturing changes also require a submission to the agency. Those can be a manufacturing site chain supplement or again, a 30 day notice. The differences that you encounter, relate to the timeframe. HDE review timeframes are generally shorter than they are for PMA. For the information relating to PMAs or for additional information relating to PMAs, we did have a PMA webinar that was held on July 26th, that you can refer to for additional information relating to what should be submitted as manufacturing information.

In the submissions there is a chart here on the slide which shows sort of a comparison and contrast and review timeframe. You know, our goal for originals and site change supplements, is 75 days versus 180 for a PMA. As many of you know, when that relates to and when that includes is a preapproval inspection, that often is a very tight timeframe in order to get a preapproval inspection done.

As it relates to modular submissions, the agency has the same 90 day review timeframe for a module. That's something that you obviously would submit before you submitted your clinical data and the Office of Device Evaluation started reviewing the clinical data. And then in 30 day notices it's the same timeframe - 30 day notices are submitted when you make a manufacturing process change that could affect the safety or effectiveness of the device.

This slide shows a link to the relevant guidance's. The same manufacturing information that you would submit in a PMA, you would also submit in an HDE. So frequently the guidance documents are either written in parallel or referred to, in order to give people an idea of what information we would be looking for, in a submission so the two guidance's that are listed here in a quality system information for certain pre-market application reviews, guidance for industry and FDA staff is one that you would look to when you're submitting an original HDE or the modular manufacturing information.

It can also be helpful in referring to that for a manufacturing site change supplement, using only the manufacturing portion of the information that's required in that guidance document and not necessarily, having to submit the design information for a site change supplement. So that can be very useful for those kinds of submissions. And then there is a separate 30 day notice and

135 day pre-market approval supplement. And the 75 day humanitarian device exemption supplement for manufacturing methods or process changes.

And that is helpful in explaining what needs to be submitted as well as what types of changes we would look for in a 30 day notice. I'll now turn it over to Greg Kittlesen.

Dr. Gregg Kittlesen: Thank you Matthew. At this point now I'll introduce myself. I'm Gregg Kittlesen, a reviewer in the neuro-diagnostics, neurosurgical devices branch. We'll be looking here at approved HDEs in our division and we see approved neurological HDEs include stents, embolics, and balloons used in neurological endovascular treatments; a neurosurgical device used to create arteriotomies during intracranial vascular bypass procedures; and neuromodulation devices.

So examples of clinical trial designs for neurological devices, many trial designs have been used to gather safety and probable benefit evidence, which supported approval of neurological device HDEs. Often prospective multicenter single arm non-randomized trial designs have been used. Study size patient numbers have been determined depending on the proposed indications for use.

Some indications for use address very small patient populations. Study duration and frequency of patient follow up are dependent on the safety questions under study and published medical treatment guidelines or common practice. Some examples of adverse events that may be observed in clinical trials of neurological devices include headache, respiratory problems, stroke, nausea, hypotension and shortness of breath. Neurologic death, major debilitating stroke, and stroke are considered severe adverse events.

Examples of probable benefit data that have been observed in clinical studies of neurological endovascular treatments include: aneurysm occlusion rate defined in this example as 100% or near complete occlusion at a pre-specified time point; observed adverse events and associated rates of adverse events; and favorable clinical outcome defined in this example as specific measures of functional independence and disability, again at a pre-specified time point.

And now we're going to turn this over to our Deputy Director, Michael Hoffman.

Michael Hoffman: Thank you Gregg. As Gregg mentioned, my name is Mike Hoffman. I'm the Deputy Director for Regulatory Policy in the Division of Neurological and Physical Medicine Devices. So I'm going to provide a few notes on the post market activities for HUDs and HDEs. So one of the key differences as (Kelly Ann) noted earlier in the presentation, is the need for IRB approvals after approval of an HDE. So after HDE approval, the device may be only used under IRB approval, after IRB approval has been obtained for use of the device at a clinical site, for the FDA approved indication, except for emergency use situations.

An HUD used in a clinical investigation is considered to be for investigational use whether or not the device is used for the HDE approved indication. Such investigational use is subject to the same requirements that apply to all FDA regulated clinical studies, including protection of human subjects and institutional review boards. If the HUD is being studied for use other than its approved indication, the IDE regulations also apply. The HDE holders are responsible for insuring that an HUD approved under an HDE is administered only in facilities having IRB oversight and acting in accordance with the agency's regulation, governing IRBs.

IRBs are responsible for initial and continuing review of the HUD. Initial review of a HUD must be performed at an IRB's convening meeting. But please note that an IRB may give blanket approval for the use of a particular HDE device at an institution, or it may be given approval on a case by case basis. Also worth noting is the pediatric advisory committee, which conducts periodic annual review of approved HUDs labeled for pediatric patients that are allowed to make profit.

The pack insures that the HDE remains appropriate for the pediatric population for which it is approved. The FDA's Office of Pediatric Therapeutics under the Office of the Commissioner, coordinates the review. The key information that should be presented to the pack, include medical device reports or MDRs, that are received since the approval, as well as other relevant safety information. They should also include a summary of any post approval studies, as well as a summary of relevant peer reviewed literature published since approval.

A key review question during the review is does the probable benefit in this profile of the device for the pediatric population, continue to support the HDE for which the exemption was granted? For more informatic about the pediatric advisory committee, please see the Web site at the bottom of the slide. Similar to - as (Kelly Ann) noted, there are also annual reports for HDEs similar to PMAs, however there are additional elements of the annual reports for HDEs that also need to be addressed.

Some of those key differences include information to support the continued qualification of the HDE, namely the updated annual incidents assessment and an explanation of why the device would not be available, unless an HDE were granted and as statement that no other comparable device is available to treat

or diagnose the disease or condition, other than another HUD approved or HUD approved under an HDE, or a device that's under an approved IDE.

You should also include an updated explanation why the probable benefits to help outweigh the risk of illness or injury from its use, take into account the probable benefits and risks of currently available devices or alternative forms of treatment. You should also include an updated amount to be charged for the device and if it is greater than \$250.00, you should provide a report by an independent certified public accountant or an attestation by a responsible individual, of the organization.

Also included is the number of devices that have been shipped or sold since the initial marketing approval. And if greater than 8000, you should provide an explanation and estimate of the number of devices that are used per patient. Finally, information should also include the clinical experience of the approved device, including any safe information that is known or reasonably to be known, by the applicant, as well as any medical device report that is filed under 21 CFR 803. As well, you should provide a summary of any changes made to the device in accordance with the supplement submitted under 21 CFR 814.108.

As noted in previous slides, post HDE approval does require assessment of use annually, to determine that the device is still eligible for the HUD and HDE programs. However, we recommend that manufacturers do this annually, not only to satisfy FDA requirements, but to also see what information is available on the use of the device, to look to the future and if warranted, look at ways to explore new or expanded indications or other regulatory pathways for the approved indications such as a PMA.

There are examples of HDE devices that have subsequently been approved under a PMA in the future, after the HDE population grows beyond the 8000 incidents or more often, the expanding - expanding the HDE indication after further studies. Additionally, some issue are converted to PMAs after manufacturers seek to remove some of the limitations that are on the HDE program. It is possible to use the HDE as a process and stepping stone toward expanding indications after further evidence gathering.

However, as noted, the regulatory bar is higher for PMAs, thus more evidence is needed to support the PMA compared to an HDE. If you are looking to use an HDE as an initial step, or if you are exploring ways to expand your currently approved HDE into other indications and potentially, a different type of regulatory pathway, such as a PMA or a de novo, please come talk to us by submitting a pre-submission to discuss your regulatory plan, so that we may provide feedback and provide clarity on the least burdensome path and recommendations to bring your device to market.

I will now turn the presentation over to Dr. Pena, for some closing remarks.

Dr. Carlos Pena: Thanks Mike. So a few closing remarks, as we look at information about our division and industry and consumer education, to obtain more information. As Mike mentioned, the best way to engage going forward, about HDEs if interested, are via the pre-submission pathway. Not only do they allow for a free opportunity to engage our staff, but sponsors and developers can help exact investments help make business decisions and they can help enable realistic expectations about next steps in moving real product to the marketplace.

Two, there are a variety of ways to learn about FDA and HDEs, from recent articles we have published to our neurological devices Web site online, to

today's webinar on HDEs as well as prior webinars on the investigation device exemption, clinical studies phase of development, PMAs and the de novo regulatory pathway. And last, find out more about FDA. If you think it's too early to contact us, that is exactly the right time to contact us, whether it be about the non-clinical work needed to move to clinical studies, the right clinical studies, to gather data about your device for an HDE, or the requirements to move your products to marketplace.

The more communication we have, the better you are moving products to patients and caregivers, and I think you'll be pleasantly surprised about the engagement with FDA. With that, I would like to turn it back to Irene, for a Q&A session.

Irene Aihie: Operator, we'll now take questions.

Coordinator: Thank you. We'll begin the question and answer session. If you would like to ask a question, or make a comment from the phones, please press star 1, make sure your phone is unmuted and record your name to introduce your question. To withdraw that request, you may press star 2. Once again, for a question or a comment from the phones, please press star 1 and record your name at this time. One moment while we standby for questions or comments.

Dr. Carlos Pena: So while we're waiting, this is Carlos. You know, one question that might have - or a couple of questions actually that we get, is often sponsors will ask us what type - specifically what type of non-clinical information is needed to get an HDE approved. Or exactly how many patients do I need to start the study? Or how many patients do I need to get an HDE approved. And to all those questions requires a little bit deeper dive into your device, the patient or population you're studying, the indications for use, the study design as appropriate, as well as other technical questions that would all be best

addressed in a pre-submission. So again, you know, these types of detailed questions, it'd be great to have an open dialog with the agency via the pre-submission process which is a free process to all.

Coordinator: And we do have a question from the phones. Are you ready for that at this time?

Dr. Carlos Pena: Yes.

Irene Aihie: Yes.

Coordinator: Thank you. Our first question or comment from the phones is from (Tom Oxley). Your line is open.

(Tom Oxley): Hello everyone. Thank you very much for the webinar. It was very informative. I'm going to be cheeky enough to ask three questions. Do you want me to ask them all at once or should we do one at a time?

Irene Aihie: One at a time would be helpful.

(Tom Oxley): Okay. So the first one is given the limitations on the intended use for an HDE and given that you're saying that the data from the HDE supported trial can be used into a future PMA submission, what is the impact of the expanded indication or the potential expanded indication into a PMA on the use of that data or the PMA, given that I guess my question is would you consider the inclusion of clinical data from the HDE, into the submission of the PMA, as a consideration of the total number of patients required in this study?

Dr. Carlos Pena: So I can start off and if there are other - we have a lot of folks around the table. You could definitely use the clinical data as part of your submission.

Again, it would depend upon what type of data you've collected and how it will be applied to the expanded use. But definitely, that would be something we would look at closely.

Josh Nipper: This is Josh Nipper. I'm the Director of PMA and HDE programs in the Office of Device Evaluation. And just to add onto what DR. Pena said, you know, a PMA can certainly cross reference the existing HDE data. You know, good clinical trial design issues are going to apply with respect to potential data pooling and whether or not, you know, the same patient populations were studied and things like that. But the data from an HDE can certainly be leveraged both preclinical and clinical data.

So if your goal is to move from an HDE to a PMA and you've already done a lot of the bench testings, you know, that data does not need to be recollected or redone. You can certainly reference the old data.

(Tom Oxley): Excellent. Thank you. My second question was I had heard that there had been changes on the definition of restriction of profit and annual reporting from the 21st Century CURES Act. But I got the impression from your presentation that that's not the case.

Josh Nipper: Again, this is Josh Nipper - 21st Century CURES did not change the profit eligibilities with respect to HDEs, that I'm aware of. And I've been pretty involved with the implementation of that, so I think that's been consistent.

(Tom Oxley): Thank you. And my last question was what is the best - what do you guys consider the best resource for the delving into and determining epidemiological populations for HDE applications? Do we just use peer reviewed journals that have looked at epidemiological data? Or are there particular references that you would prefer to see?

Dr. Carlos Pena: That's a good question. I think, you know, it really depends upon - I don't think we have a preference for one or another. It really depends upon what your device is and how does your device intend to be used and putting your package together and especially having that pre-submission beforehand, where you - we would help share with you how to present and put your package together for an HDE submission.

(Tom Oxley): Thank you.

Coordinator: Thank you. And again, as a reminder, for questions or comments from the phones, it is star 1. Make sure your phone is unmuted and record your name to introduce your question. To withdraw that request, you may press star 2. Once again, for questions or comments from the phones, please press star 1 at this time. One moment, while we standby for questions or comments. And again, that's star 1 and record your name for a question or a comment. One moment please. Thank you. And our next question comes from (Brandon Shepherd). Your line is open.

(Brandon Shepherd): Hi. This is probably a straightforward one, but I was just curious as to why the criteria changed from 4000 to 8000 with respect to HDE designations.

Josh Nipper: Well the criteria - this is Josh Nipper again. The criteria was changed by Congress at the passing of 21st Century CURES a little over a year ago. You know, I think the intent is to get, you know, safe and effective medical devices out to the public. And the 4000 limit was fairly restrictive. It's a very small patient population. And so I think the idea was to, you know, allow for slightly expanded access. I mean examples include things like cerebral palsy,

where the patient population was over 4000, but could probably fit within a broader scope.

So I think it was essentially just an expansion of the program to hopefully reach additional patients.

Irene Aihie: We'll take our next question.

Coordinator: Thank you. Our next question or comment comes from (Ming Chen Chu). Your line is open.

(Ming Chen Chu): Hi. We just had a quick question about the approval timeline. We noticed that the modular HDE application had a 90 day review versus the normal 75. Why is that? And what's the advantage of doing a modular over the original then?

John Nipper: Again, this is Josh. A modular allows the review division to begin looking at some of the preclinical and technical information that may be finished prior to completion of your clinical data. So once the final module which is almost always a clinical module, is submitted, it is converted into a traditional HDE and has a 75 day clock. The benefit to going the modular route is the division may have already reviewed things like biocompatibility or software information and may have already given feedback for those pieces. And so therefore, may have less questions when it comes to looking at the HDE when it's first reviewed.

So once the clinical is submitted it may be a more straightforward process and you may have kind of a cleaner look at only the clinical information, as opposed to mixing a bunch of different preclinical or other even manufacturing issues.

(Ming Chen Chu): Okay. So the 90 day starts when the first module is submitted?

Josh Nipper: So it's 90 days for each module that you would submit. And companies can pick sometimes modules are two or three and sometimes, you know, they're five or six depending on kind of how long it takes you to develop your device and how many - how much you want to break it apart. But the 90 day clock is for the individual modules. But once the clinical data is submitted, it would convert to an original HDE with a 75 day clock.

(Ming Chen Chu): Okay. Thank you.

Coordinator: Thank you. And again, as a reminder, it is star 1 and record your name for a question or comment, and star 2 to withdraw that request. Our next question or comment comes from (Carol McPherson). Your line is open.

(Carol McPherson): Hi. I have two questions. And the first one you may have already addressed; I apologize if you did. The change from 4000 patients to 8000 - so the FAQ for HDE holders and IRBs and clinical investigators, etc. the 2010 document is still the currently approve document. Correct?

Josh Nipper: That is correct, although the 4000 to 8000 is a guidance document and it's non-legally binding. The 4000 to 8000 was implemented immediately under the passing of 21st Century CURES. So we are - we have changed the operation, excuse me, of that, to 8000.

(Carol McPherson): Okay. Great. And then my next question is for clinical sites that use the IRB approved HUDs, HDEs, does the FDA ever audit clinical sites?

Matthew Krueger: This is Matthew Krueger. I'm with the Office of Compliance, but I admit that I'm not actually in the bioresearch monitoring division. So I mean I think, you know, generally my understanding of bioresearch monitoring is they do audit clinical investigators. They do audit sites and IRBs that are responsible for, you know, maintaining the integrity of clinical studies or those kinds of patient protections. And that's really what they're geared towards is patient protection measures and that's really the function of the IRB.

So they do audit them. You know, I couldn't speak at this time to, you know, what kind of frequency they do that on a routine basis, but I know that if there is for some reason, a for cause basis or they believe that there is, you know, or there is an allegation of some kind of malfeasance or something, the agency does have the authority and can inspect as required or as needed. You know, we obviously do, as a part of our preapproval review process, we do also in applications that have clinical data, we frequently do.

Although it may or may not be utilized in every application. Exercise a role to perform oversight and just insure that the data submitted to the agency, you know, meets good clinical practice requirement and so we do exercise that as well. Hopefully that answers your question. I think if you have more specific questions, that really would be something I would encourage you to submit to the email address that's on the last slide, so we can give you more specific information.

(Carol McPherson): Great. Thank you so much.

Coordinator: Thank you. And again, as a reminder, for any further questions at this time from the phones, please press star 1, make sure your phone is unmuted and record your name. And to withdraw that request, it is star 2. Once again, for final questions or comments, please press star 1 at this time. One moment

while we standby for any questions or comments. And I am currently showing no further questions or comments. I'd like to turn it back over to our speakers for any closing remarks.

Irene Aihie: Thank you. This is Irene Aihie. We appreciate your participation and thoughtful questions. Today's presentation and transcript will be made available on the CDRH Learn Web page at www.FDA.gov/Training/CDRHLearn, by Thursday, January 4th. 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, immediately following the conclusion of today's live webinar.

Again, thank you for participating and this concludes today's webinar.

Coordinator: Thank you. That does conclude today's conference call. Thank you for your participation. You may disconnect at this time.

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