

FDA Webinar: Humanitarian Device Exemption Program

Moderator: Irene Aihie
October 21, 2019
12:00 pm ET

Coordinator: Welcome and thank you for standing by. At this time, all participants are in a listen-only mode until the question and answer session.

Today's conference is being recorded. If you have any objections, you may disconnect at this time.

I will now introduce your conference host, Ms. Irene Aihie. 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. On September 6, 2019, the FDA issued a Final Guidance on the Humanitarian Device Exemption Program. This guidance provides clarity to industry and FDA staff about the current review practices for the Humanitarian Device Exemption Program. This programmatic guidance addresses commonly asked questions about HDEs and Humanitarian Use Devices, including FDA actions on HDE applications, post-approval requirements, and special considerations for devices marketed under the HDE Program.

Today, Stephanie Shedd, Biomedical Engineer, in the Office of Product Evaluation and Quality here in CDRH, will present an overview of the guidance document. Following the presentation, we will open the line for your questions related to information provided during the presentation. Additionally, there are other Center subject matter experts here with us today to assist with the Q&A portion of our webinar.

Now, I give you Stephanie...

Stephanie Shedd: Thank you, Irene. Hello, my name is Stephanie Shedd. I am a biomedical engineer in OHT6, the Office of Orthopedic Devices. I'm here today to discuss the recently issued guidance on the Humanitarian Device Exemption or HDE program which I worked on while I was on temporary assignment as a policy analyst to the Division of Submission Support in the Office of Regulatory Programs in the Office of Product Evaluation and Quality in CDRH.

Today's agenda includes definitions and objections relevant to today's webinar, a brief background of the HDE program, the scope of the recently published guidance document, the expected content, review steps, and timeline of an HDE application, post-approval requirements for an approved HDE, special considerations for HUD use under HDE, a summary of significant changes in the HDE guidance compared to the last version, and finally resources that are available to you. We will end the webinar today with time for questions from the audience.

I'd like to define the following terms before getting further into this talk. humanitarian use device or HUD is medical device that is intended to benefit patients in the treatment or diagnosis of diseases or conditions that affect or are manifested in not more than 8000 individuals in the US per year. A

Humanitarian Device Exemption or HDE is the marketing application for a HUD. These applications are exempt from the effectiveness requirement of the Safe Medical Devices Act and are subject to certain profit and use restrictions as we'll go over later in this talk.

An Institutional Review Board or IRB is responsible for, among other things, the oversight of the use of HUDs at medical facilities per the FDA regulations that govern IRBs. An appropriate local committee is defined in the guidance as a standing committee at a medical facility that has expertise and experience in reviewing and making treatment decisions for clinical care especially in the area of rare diseases.

Our objectives for this webinar today are to provide an overview of the scope of the HDE program as described in the guidance document which was issued on September 6th and to review significant changes in the most recent guidance document which supersedes the prior version that was issued back in July 2010.

The HDE program has evolved over time and encourage the development of devices designed to treat or diagnose rare conditions. In 1990, the Safe Medical Devices Act included a provision to exempt qualifying devices from the requirement to demonstrate a reasonable assurance of effectiveness per Section 514 and 515 of the Food, Drug and Cosmetic Act.

In 1997, the FDA Modernization Act allowed for the use of HUDs approved under an HDE at medical facilities without prior IRB approval in certain emergency situations. In 2007, the FDA Amendments Act allowed HUDs indicated for use in pediatric patients or in a pediatric subpopulation to be sold for profit. In 2012, the FDA Safety and Innovation Act, or FDASIA, further

expanded the eligibility of devices approved under HDE that are able to make a profit.

What brings us here today is the 21st Century Cures Act or simply Cures Act which became effective in December of 2016 and specifically calls for modifications to the HDE program. Of note, the Cures Act modifies the HUD threshold to not more than 8,000 individuals in the United States per year which is an increase in the previous threshold of 4,000 individuals. In addition, the requirements that IRBs need to approve the use of HUDs at medical facilities was revised to also include appropriate local committees. And we will discuss what that means later on in the talk.

There is a specific commitment related to the HDE program in which FDA committed to publish a draft guidance within 18 months which defines the criteria for establishing probable benefit in an HDE application. This draft was published in June of 2018. The current guidance represents the finalization of that draft guidance which incorporates responses to public comments that were received.

The scope of the guidance document encompasses most stages of the HDE review including operational aspects such as filing and substantive review, and potential decisions that can be made on an HDE application. The guidance document discusses the principal criteria that FDA uses to determine probable benefit and also how FDA will make the assessment of whether probable benefit of the HUD outweighs the risk of injury or illness from its use. In addition, post-approval requirements and special considerations specific to the HDEs are discussed. Finally, decision tools for FDA staff or for reviewing HDE applications are introduced.

For a complete HDE application to be submitted to FDA, it is important to note that the HUD designation should be submitted to and approved by our Office of Orphan Products prior to the HDE submission. This is a review from the Office of Orphan Products that agrees that the patient population is less than the threshold of 8,000 patients per year. Please see the guidance document which has also been revised recently for important considerations when applying for a HUD designation.

The filing review for an HDE application assesses the content of the submission and determines whether it is administratively complete. A filing checklist for use by industry and FDA reviewers is provided in Appendix A of the guidance. The applicant is expected to provide the information requested or provide a justification for any alternative approaches used for any of these items. The filing decision is to be made within 30 days from the date the HDE was received.

Reviewers are strongly encouraged to use interactive review to obtain any missing information either during the filing or substantive review. Thus it is a best practice for applicants to be prepared to respond to FDA requests in a timely fashion. A reviewer would expect that the following major categories and information would be provided in an administratively complete application. The device description that includes all components and accessories and their mode of action. Design drawings and specifications and materials including a citation of any applicable material standards.

The indication for use statement as proposed in the HDE should be consistent with the HUD-designated disease or condition and any changes to this language should be justified.

The HDE should contain valid scientific evidence that demonstrates the safety and probable benefit of the device. This information may include bench, animal and/or clinical data. Note that we support the principles of the three Rs, to reduce, refine and replace animal use in testing when feasible. We encourage applicants to consult with us if they wish to use a non-animal testing method and we will consider if such an alternative method could be assessed for equivalency to an animal test method.

The guidance also encourages the collection of patient preference information that may contribute to the determination of safety and probably benefit. The application should provide a discussion of why, based on the data provided, the probable benefit outweighs the risk of use of the device. The application should also include manufacturing information in accordance with the quality system regulation as well as labeling including physician and patient labeling if applicable. Note that patient labeling is often applicable especially in the pediatric patient applications.

I want to point out some elements that are unique to the filing of an HDE. As stated earlier, the HUD designation should already be obtained prior to submission of the HDE and a copy of or reference to the HUD designation letter should be provided. The amount to be charged for the device should be provided. This information should be provided regardless of device's eligibility for profit-making. If this amount exceeds \$250 , then a report must be provided verifying that the amount charged does not exceed the cost of the device's research, development, fabrication and distribution.

Information regarding comparable devices should also be provided. The applicant should conduct a search within the device space and provide a statement that no other comparable device other than a HUD approved under HDE or a HUD for use under an approved clinical investigation is available to

treat or diagnose the disease or condition. If the statement cannot be provided and there are alternative devices available, then HDE may not be an appropriate marketing pathway.

Once an application has been determined to be administratively complete via the filing review, a review of the safety of probable benefit of the device occurs during the substantive review phase. In order to demonstrate safety, the HDE application must demonstrate the device will not expose patients to an unreasonable or significant risk of illness or injury and the probable benefit to health from use of the device outweighs the risk of injury or illness from its use. Which takes into account the risks and probable benefits of currently available devices or alternative forms of treatment.

Unique to HDE review is the standard of probable benefit as HDEs are exempt from the requirement to demonstrate effectiveness which is necessary for other marketing applications such as PMA premarket approval. As defined in the guidance, probable benefit can be determined when there's evidence for FDA to reasonably conclude that patients are likely to benefit from the use of the device. This could take into account many factors including the type of benefit, the magnitude of the benefit, the probability of the patient to experience one or more of those benefits, the duration of the effects, patient perspectives, and/or a care partner such as parent or aide perspective. Many of the HDE applications are for pediatric patients, pediatric subpopulations, thus, the care partner or a parent or aide perspective are often important in the decision-making.

The reviewer's determination of whether the HDE demonstrates probable benefit includes many considerations. The reviewer may accept a greater level of uncertainty in the data as a reasonable assurance of effectiveness is not required. The reviewer may consider the intended use of the device including

the target patient population and the size of the population. For example, the smaller the patient population, the greater the uncertainty FDA would expect. The reviewer may take into account currently available alternative treatments or diagnostics and may take into account patient perspectives on risk, uncertainty and probable benefit.

In a parallel effort, there has been a lot of work on defining uncertainty in benefit-risk determinations which recently ended in a final guidance document which further describes the use of uncertainty in decision-making. We highly recommend you consult this guidance as these principles apply for HDE review as well.

Upon completion of the substantive review, an FDA action is to be made within 75 days of the receipt of the submission. The guidance discusses the following major actions; approval order, approvable order, major deficiency letter, not approvable letter, or denial order. Major amendments including responses to a request for additional information letter will extend review time up to 75 additional days. In addition, a submission is considered voluntarily withdrawn if there is a failure to respond to any request for additional information such as a filing or major deficiency letter within 75 days unless an extension is granted. An extension may be granted to respond up to 360 days from the date of the additional information request.

Once an HDE is approved, it is subject to several requirements unique to HDEs. An IRB must provide oversight at medical facilities where HUDs are used. The statutory language now allows either an IRB or an appropriate local committee or ALC to review and approve the use of a HUD to treat or diagnose patients at that facility. An appropriate local committee may include a standing committee at the facility that includes physicians with experience

and the treatment of rare diseases or conditions, as we'll discuss further in the next slide.

It's important to note here that approval for individual HUD use is not required. A generalized approval may be granted for this facility. Also the use of an ALC does not change the provision that for certain emergency uses prior approval by an IRB or appropriate local committee is not required.

An appropriate local committee is defined in the guidance as a standing committee for the facility that has expertise and experience in reviewing and making treatment decisions for clinical care, particularly in applying innovative medical device technologies to clinical care.

The committee may include physicians with experience and treatment of rare diseases or conditions. Examples of these types of committees which may already exist within a facility include a peer review committee, credentialing committee or quality care committee.

The guidance also provides recommendations for IRB or ALC review of an application for HUD use at their facility. FDA recommends the review of the following information at a convened meeting of the committee; a copy of the HDE approval order, a description of the device, the product labeling, the patient information packet that may accompany the HUD, a sample consent form for the use of the HUD in clinical care if required by the IRB or ALC or by the facility policy. A summary of how the physician proposes to use the device include a description of any screening procedures, the HUD procedure and any patient follow-up visits, tests, or procedures. Not everything on this list may apply in all circumstances, but it is to be used as guideline.

Additional post-approval requirements unique to HDE include reporting of adverse events. All adverse events associated with use of the HUD whether expected or not, must be reported and evaluated in accordance with the medical device reporting requirements in 21 CFR Part 803. Specifically device manufacturers and user facilities should report - should submit reports to FDA and the IRB or appropriate local committee that approves the use of the HUD. In addition, adverse events that occur in HUD that are approved and labeled for pediatric patients or a pediatric subpopulation and are also exempt from the profit prohibition are reviewed periodically by the FDA's pediatric advisory committee or PAC.

Additional requirements unique to approved HDEs include the submission of HDE supplements to modify the approved device. Supplements generally follow the review guidelines for PMA with some changes to the review timeline. However, it is important to note that any request for new indications should be accompanied by a new HUD designation through the Office of Orphan Products.

Periodic reports, which are often annual reports, are specified in the approval order and are to be submitted post-approval. For HDEs these reports should include updated information to demonstrate that the HUD designation is still valid, and the patient population has not changed. In addition an updated discussion of comparable devices should be provided and an explanation of why the device would otherwise not be available without the HDE approval, to make sure the HDE approval is still valid.

Similar to a PMA approval, a post-approval study may be required as a condition of approval to understand long term performance or evaluate the learning curve or training issues associated with the use of the device. A full protocol or a protocol outline including the relevant enrollment, follow-up and

reporting timepoints is agreed upon prior to HDE approval. If only a protocol outline is agreed upon at time of approval, a full protocol may be developed following approval in a protocol supplement to the HDE.

Recommendations for developing and conducting post-approval studies are outlined in the guidance document “Procedures for handling post-approval studies imposed by PMA order.” While this document is specific to PMA, much of the processes are similar for HDE post-approval studies.

Next we will discuss special considerations for HDE holders when marketing their device. First we will discuss profitability. HUDs under an HDE cannot be sold for an amount that exceeds the cost of research and development, fabrication and distribution of the device, in other words for profit, unless the patient population fits the following unique circumstances. The device is intended and labeled only for pediatric patients or in a pediatric subpopulation. The disease does not occur in any pediatric population or pediatric sub-groups. For example this could be a population susceptible to age-based disease such as Alzheimer's, which is not a HUD qualifying condition, but is used here as an example. Or the disease or condition occurs in pediatric patients in such numbers that the development of the device for such patients is impossible, highly impracticable, or unsafe.

The definitions and examples illustrating the terms in possible, highly impracticable and unsafe are provided in the guidance. For example geographic dispersion of patients and/or sites would likely not be considered impossible or highly impracticable because of the speed and efficiency of modern communication tools and would not be considered an extraordinary circumstance. The applicant should provide adequate supporting documentation in the HDE to support the request for exemption from the profit prohibition.

A special consideration for HDE holders includes the annual distribution number or ADN. If eligible, the HUD can be sold for profit up until the number of devices sold excess the ADN. If the HDE application or supplement, I'm sorry. In the HDE application or supplement, the applicant should provide the number of devices per year that are reasonably needed in order to treat the conditions in each individual and provide adequate documentation to support such number. The ADM will be greater to, I'm sorry. The ADM will be equal to or greater than 8,000 depending on how many devices per year are reasonably needed to treat, diagnose or cure an individual.

For example, if two devices are needed, then the ADN is 16,000 and the HDE holder can sell up to 16,000 devices for profit per year. Once the ADN has been exceeded, then the sales for the HUD for the remainder of the year are subject to the general prohibition on profit. Unless the FDA approves an ADN modification request in an HDE supplement.

A special consideration for HDE holders includes the information that's provided to patients and in the labeling. FDA does not require informed consent from the patient that is being treated or diagnosed with an HDE approved HUD as it is considered an approved device. However, the IRB or ALC may choose to require additional information be provided to patients or informed consent to be obtained. Should written documents be provided to patients, much of the information that was approved under the HDE and the patient labeling should be included.

In addition, all labeling documents should be truthful and non-misleading. As required in the regulation, the labeling should include the statement that this is a humanitarian device, authorized by federal law, for use in treatment or

diagnosis of a disease or condition and that the effectiveness of this use has not been demonstrated.

A special consideration for HDE holders includes those for pediatric use. Pediatric is defined by the FD&C Act as patients who are 21 years or younger that means up to but not including their 22nd birthday at the time of, sorry, at the time of diagnosis or treatment. As discussed previously, HUD labeled for use in pediatric patients or in a pediatric subpopulation may be eligible to be sold for profit.

An HDE application may be intended for use in both pediatric and adult populations. In that case, an application should include data supporting the use in both pediatric and adult populations. Or an appropriate rationale that addresses how the data provided for one population are sufficient to support approval of an HDE application with indications for use in both populations. For example, how an adult dataset supports both adult and pediatric use.

Additionally, HUDs approved via HDE for pediatric populations are required to be reviewed annually by the pediatric advisory committee or PAC. This committee advises the FDA commissioner on emerging issues in pediatric research and reported adverse events, or other information of interest.

This review ensures that the HDE remains appropriate for the pediatric populations for which it was approved. The PAC also conducts periodic review of adverse events for HUDs when they are exempt from the profit prohibition. Additional information on PAC membership tasks and upcoming meetings are available on FDA's website at the link shown here and their last meeting was in April of 2019.

So finally, transitioning over to the HDE reviewer tool. The guidance provides several tools for use by FDA reviewers during the review of an HDE application. Of note, the filing checklist is incorporated into the guidance and is provided in Appendix A. The checklist format helps to ensure that the application contains the necessary information to conduct a substantive review. The elements on the checklist stem from either statutory or regulatory requirements and the checklist also includes some elements that alone would not be the basis for a refuse to file but FDA strongly recommends providing in order to facilitate substantive review and avoid significant delay of review of the submission. For example, providing sections that are key articles in English. Generally the format and content of the filing checklist are consistent with the analogous checklist for other types of premarket submission. For example, the PMA RTA checklist.

Concerns identified by the agency regarding results and outcomes of nonclinical and clinical studies to should be addressed in the substantive review and should not preclude a filing decision. In other words, the FDA should not refuse to file an HDE application because we have reviewed the data and believe that the application is ultimately inadequate to meet the standard for HDE approval. This should be addressed in the substantive review.

Additional tools provided in the guidance include Considerations for the Probable Benefit-Risk Assessment in Appendix B and Probable Benefit-Risk Assessment Summary in Appendix C. These worksheets provide flexibility and use of scientific judgment in assessing totality of evidence to determine if a specific device meets the standard for HDE approval.

They were designed to allow FDA to take into account considerations relevant to HDE applications, for example a relatively small patient population, under

a framework that is consistent across device marketing submissions, for example, a PMA. These worksheets prompt reviewers to consider specific criteria for probable benefit, risk, and sources of uncertainty when evaluating the data provided.

So in summary, the guidance provides several updates to the HDE process in order to facilitate innovation and development of devices for rare diseases and conditions. Per the Cures Act a HUD is now defined as a device for use in a patient population that does not exceed 8,000 patients per year. This is a larger threshold compared to the previous 4,000 patients per year.

The final guidance provides definitions and criteria for determining probable benefit and assessing whether the probable benefit outweighs the risk of use in a more consistent and more predictable manner. The guidance allows more flexibility in use of appropriate local committees in addition to the IRBs to approve HUD use at medical facilities. And the guidance provides reviewer tools to ensure consistency as well as flexibility in reviewer decision-making.

So this is a busy slide, but we wanted to make you aware of a small sample of the resources that are appropriate to use when developing an HDE application. As discussed earlier, PMA-related resources may be beneficial in certain situations. In addition, several concepts such as benefit risk and uncertainty were developed in parallel with this guidance and were incorporated into this HDE guidance and review process.

So this concludes our presentation and we're now available for any questions from the audience.

Coordinator: We will now begin our formal question and answer session. If you have a question, please press Star 1 on your touchtone phone. Only record your first

and last name. To withdraw your question, you may press Star 2. So once again, to ask a question, please press Star 1 on your touchtone phone. One moment for the first question.

Stephanie Shedd: Okay, so while the operator is queuing up some questions, I wanted to introduce my co-presenter. I'm here with Josh Nipper. He's the Director of the Division of Submission Support within OPEC.

Josh Nipper: Thank you.

Stephanie Shedd: And one of the most frequently asked questions that we get, the question, isn't it burdensome for IRBs to have to approve each use of a HUD at their facility? And the answer is that the IRBs or the ALCs do not have to approve each individual use. They may provide a blanket approval for any patient that's deemed appropriate for treatment with that HUD at their facility.

Do we have any questions? Another frequently asked question that we get. How many HDEs are approved each year? So we generally approve two to five HDE applications per year. And we have approved about 76 since the program was started in 1990. The FDA website keeps a list of recently approved HDEs for you to take a look at.

Woman: We'll take our first question.

Coordinator: The first question is coming from (Kim Jaffrey). You may ask your question.

(Kim Jaffrey): Hi there. I was wondering. Would the FDA allow a device under the HUD to be used with an unapproved but clinically tested therapy? Or if the device needs to be used with an already approved therapy?

Josh Nipper: So when you say therapy are you referring to like a pharmaceutical or a drug? If so, I would say, you know, in order to be approved under the HDE application, everything would need to be approved or on label. We do have HDEs that are used with a drug or a biologic. But those drugs or biologics are legally marketed therapies. So I'm not sure if that was your question or not.

Coordinator: Once again, if you do have a question, please press Star 1 on your touchtone phone. The next question is coming from Mr. (McDonald). Your line is open.

Mr. (McDonald): Thank you. I had the question about the language regarding IRBs and ALCs. And the question is, in a facility not affiliated with an institution, and so they have no established IRB, but they do have a standing ALC, how would IRB oversight be completed and documented?

Stephanie Shedd: You know, you're right. There is a distinction between IRB oversight at a facility versus use of the HDE approved device in certain cases. So yes, the facility needs to have that IRB oversight and then the IRB or an appropriate local committee can review the individual cases for the HDE use.

Josh Nipper: Yes, I would agree. Every - to use at a facility, the facility must have IRB oversight according to the statute. That's not to say that the IRB has to review the use of that. It could be an appropriate local committee, but there does have to be an IRB in place at the facility. It can be a sort of a national or central IRB. So there, you know, we're aware that there are national level IRBs that approve or that oversee facilities across the country. And that's perfectly fine. It doesn't have to be a local, you know, in-house IRB, but there does need to be IRB oversight.

((Crosstalk))

Coordinator: Once again, if you do have a question, please press Star 1 on your touchtone phone. The next question is coming from (Kathy Moore). Your line is open.

(Kathy Moore): Hi there. So if we understand correctly from the slides, ALC can review the HUD alternatively from an IRB. Is that correct?

Stephanie Shedd: Yes, that's correct.

(Kathy Moore): How should the - how should we verify that the ALC is constituted appropriately? I think for IRBs we need to be looking for IRB roster or an FWA assurance statement? If I understand correctly, you're not requiring an IRB to review it. It can be an ALC. So how do we ensure that ALC is appropriately constituted?

Josh Nipper: So that's a great question and not one that is clearly spelled out in the Act or even in our guidance. You know, my best advice is that manufacturers and HDE holders ask those questions. And so if a facility is using an appropriate local committee, I believe the manufacturer should verify that it - they believe it's appropriate. There - when those provisions were put into the Act, there wasn't a lot of clear direction as to what constituted an ALC. FDA has attempted to provide some examples of that. And we're fairly clear that those examples should include people either familiar with the clinical specialty or with a rare disease type patient population.

But we don't provide, you know, clear stipulations. You know, as I'm sure aware, IRB rosters and procedures are more spelled out in the regulations and this ALC language was somewhat new to us as well. We honestly think they should be operated fairly close to that of an IRB, but there could be some differences that we're aware of.

Coordinator: One again if you do have a question, please press Star 1 on your touchtone phone. The next question is coming from (Pata). Your line is open.

(Pata): Hi there. Once clinical data is obtained post HDE for a HUD device, then at some point can those be converted to a PMA for standard indication based on patient data obtained during this forced HDE process?

Stephanie Shedd: Yes, that is a potential pathway. It's most likely that once an HDE is approved, it goes on to collect additional data which is then used to meet the standard for a PMA approval which is safety and effectiveness. So most likely that includes additional or broader dataset to support that effectiveness definition.

(Pata): So but we can just take that data then and assuming we have enough data to support this new broad indication and by sort of PMA based on the data then?

Josh Nipper: Yes, I mean there have been multiple instances in the past where a sponsor of an HDE continues to collect data either through a post-approval study or on their own behest. And collects additional data and gets to the point where they believe they can prove effectiveness as opposed to probable benefit. And they come in and there have been 5 or 10 examples where we've had an HDE that went onto get PMA.

(Pata): Thank you.

Coordinator: The next question is coming from (Allison Komiyama). Your line is open.

(Allison Komiyama): Hi, thank you so much for this presentation. Actually the last caller, you answered my question within your response. I was going to ask how many have gone onto have a successful PMA. And the answer is about 5 to 10. So

and you said there were about 70 or 80 that have been approved? Is that correct?

Stephanie Shedd: Yes, that's correct, about 76 since 1990.

(Allison Komiyama): Okay, thank you. Thanks to the last caller.

Coordinator: The next question is coming from (Sherry Shambley). Your line is open.

(Sherry Shambley): Hi, thank you for this webinar, very informative and quite timely. My question for you today is approximately how many patients would be recommended by the FDA in an HDE study?

Stephanie Shedd: I mean that's going to vary case-to-case. It's going to come down to the intended patient population for the device as well as that idea of uncertainty. How many patients will be determined by how much uncertainty will be acceptable within that application. You're going to have examples where you want less uncertainty. An example is where, you know, endpoint is mortality versus perhaps more uncertainty would be acceptable in an indication where the endpoint is pain.

So it's hard to dictate an exact number. It may not be statistically powered, I'll put it that way. But you're still going to need enough information to create that standard of probable benefit via valid scientific evidence.

Josh Nipper: I agree completely, and I would also say, you know, there is safety threshold as well. And there, you know, the probable benefit is kind of a key differential from other areas. But you do need to demonstrate some, more than some, you do need to demonstrate safety of the device as well. And so often an HDE study will be, I don't want to use the word powered because that may

overstate it but centered around collecting enough safety information to prove that, you know, the device is safe for use.

You know, my best advice for companies exploiting the pathway is to come in with a pre-submission. Discuss with the FDA review team what their expectations may be for an HDE type study because as (Stephanie) said, it's incredibly variable. I've seen very small studies for patient populations that are very small. Then I've seen them where they are almost PMA like for some of the HDE populations that kind of get up close to that threshold.

So that's a very difficult question to answer and I guess our answer is it depends.

(Sherry Shambley): Thank you.

Coordinator: Once again, if you do have a question, please press Star 1 on your touchtone phone. The next question is coming from (Erika). Your line is open.

(Erika): Hi. This is (Erika) and from the IRB perspective we were, I think, all very excited to find that we could give this duty to another committee. However, you've explained that IRBs remain responsible for oversight which sounds to me like we now have two committees instead of one doing something that we really don't understand fully. So could you explain what the difference is between the appropriate local committee doing review and the IRB now doing oversight? What do you mean by those terms?

Josh Nipper: Great question, and as far as the oversight goes, the Act specifically states that a - to be - for an HDE to be used a facility, they must have IRB oversight. What the IRB decides to defer down to the appropriate local committee is really kind of up to them. So I would say that an IRB could review the, you

know, there was a question earlier about the, you know, the makeup or constitution of those appropriate local committees. That could be what the IRB looks at. They could say you want to make sure that that ALC has an appropriate makeup, but not necessarily review the merits of the HDE. They could, you know, they could both if they wanted to be very hands-on. Or they could just say, you know, the ALC language is somewhat confusing which we acknowledge. And, you know, continue to provide direct oversight of the HDE study.

You know, we've heard from some IRBs that's their intent. They don't want to, you know, defer this responsibility and that's perfectly within their right and purview.

Stephanie Shedd: Right, I mean the IRB oversight includes stuff that's applicable across the use of devices at the facility. So is there appropriate informed consent? Is there appropriate communication with the patient? And then can, as (Josh) said they can delegate down certain responsibilities and to the ALC such as reviewing the HDE approval and that specific material and whether use of that device is applicable to the patient that's currently being reviewed.

So it's additional flexibility within the facility that doesn't necessarily need to be used, if that makes sense.

Coordinator: The next question is coming from (Angelique Gupta). Your line is open.

(Angelique Gupta): Hi, thanks. My question is regarding the ADN or the annual distribution number. I was just wondering that you didn't get an ADN assigned on approval. And maybe not in subsequent annual reports and you don't have one. Under what circumstances would you be assigned an AND?

Stephanie Shedd: You would be assigned an ADN. That would be part of the approval order at the time of HDE approval. And you can request an update to that ADN at any time via supplement to the HDE.

Josh Nipper: To be clear, the ADN is only required if you're requesting profit. So if you, you know, if you're an HDE which, to be clear, most are, if you're an HDE that occurs in adults and pediatrics and you don't have that pediatric data, then, you know, you're prohibited from making a profit. And the ADN rules essentially don't apply. If you are ...

(Angelique Gupta): Okay.

Josh Nipper: ... pediatric only or you've requested and provided enough documentation to demonstrate that you don't you know, that you fell within one of the other two criteria, then you'll be assigned an ADN at the time of either approval if you're requesting a profit when you submit, or you can submit a subsequent supplement and request to make a profit. And request an ADN and we will evaluate that and basically, you know, if we agree that you meet the criteria for earning a profit, we will put that in the letter and then assign an ADN at that time.

(Angelique Gupta): Okay, thank you.

Coordinator: And the next question is coming from (Mahe). Your line is open.

(May): Hello, this is actually (May). Hi. I was going to ask the same question that (Angelique) just asked. And but I just wanted to clarify that the profitability exemption is really only for pediatric applications. Is that correct?

Stephanie Shedd: Most likely it's a pediatric application, but that's second criteria. It's for - the example is an age-related condition such as Alzheimer's with no chance for a pediatric patient to be included. But it's only that adult population. That also could be eligible for profit-making.

(May): So thank you for that.

Josh Nipper: (Unintelligible).

(May): Sorry, so sorry.

Josh Nipper: (Unintelligible), I'm sorry. Go ahead.

(May): No, I think you were about to just answer my question and that was if this particular disease did not occur in pediatrics and occurs in specific adult populations and occurs in a small part of the population and it has been eligible for an HDE, would it still be possible to be - to apply for an ADN even if there's very little application in pediatrics? (Unintelligible).

Josh Nipper: Well, so very little and none is different.

(May): Pardon:

Josh Nipper: So, very little in pediatrics and none in pediatrics are different.

: If you can - if a sponsor can prove that there is no pediatrics, you know, through established literature, if they can prove that it's just doesn't or can't occur in pediatrics, then they can earn a profit. If it's very small number in pediatrics, they either have to provide data to show that the HDE can be used

for that subset. Or provide a justification saying like it's basically impossible to study pediatrics because it's so small.

We've approved that kind of final clarification a couple of times, but I can tell you we're fairly critical of that, you know, when sponsors try to justify that. I mean if it exists in the pediatric subpopulation, we are trying to get them to study in those populations. But I mean on your comment, I think very little and none are different categories within the Act.

(May): That is great to know. Thank you very much. I really appreciate that distinction. Thank you.

Coordinator: Once again, if you do have a question, please press Star 1 on your touchtone phone. The next questions is coming from (Sherry). Your line is open.

(Sherry): Hi, thank you again for the additional question. For the 5 to 10 HDEs which later become PMAs, did they require an amended or supplemented indication for use? I understand the difference just between the safety and the efficacy, but does it require a different indication for use between the two applications?

Josh Nipper: I'm not 100% sure I understand your question. But in order to go from HDE to PMA, the sponsor would need to submit a full PMA. And that includes user fee. It includes, you know, submission of any additional data they've collected. They could choose to - it's really up to the sponsor. They could choose the identical indication of the HDE. They have additional data. They could extend that outward and say, you know, so if the HDE were for only, you know, making this up, but only Class 3 and 4 condition. And the PMA had data for Classes 1, 2, 3 and 4. The PMA could have that additional broader indication. It would really be up to the sponsor and depend on kind of the data they selected.

(Sherry): Thank you.

Coordinator: The next question is coming from (Judy). Your line is open.

(Judy): Yes, hi thank you. Could you speak to the reporting requirements for off-label use such as reporting to sponsors and reporting to IRBs?

Stephanie Shedd: Yes, the guidance goes into a little bit. You know, we're not here to dictate practice in medicine. The surgeons can use the device as they see fit. If it does come to reach a threshold where that off-label use is going to require marketing application, then yes, the surgeons, the users of the device should be reporting back to the sponsors. And the sponsors would then prepare the marketing application for that off-label use. That's one of the expectations.

Josh Nipper: Yes, I mean to add on a little. It's up to the IRB would they approve their use for. Some IRBs have been very strict and only approve it for on-label. And then basically say off-label use is not allowed at their facility. That their - that's the IRB's prerogative. They can do that. Others are fairly broad and say, you know, it's up to the physician to use it how they see fit. But physician is not inherently required to report that to their IRB or their sponsor or the manufacturer. You know, it's a best practice for them to summarize the use. To say, you know, here's how they, you know, at least to their IRB, here's how we're using the device and the results we've seen. But it's not, you know, we - FDA does not regulate practice of medicine and so it's not inherently a requirement to report that to the IRB, to the company or to us for that matter.

(Judy): Thank you very much.

Coordinator: And the next question is coming from (Maria). Your line is open.

(Maria): Hello, I'd like to understand, or can you comment if the pre-submission program, Q-Sub program is useful during the HDE process the same what that it's or similar way that it's used during the 510K process? Or well of course during the PMA process it's usually required. But I'm just not sure due to the process, the HDE process itself, whether a pre-sub is actually useful?

Stephanie Shedd: Yes, we strongly recommend use of the pre-sub process. That could come before or after the HUD designation. That's kind of an independent process through the Office of Orphan Products. But the pre-submission process through your OHT or your review office could be very helpful in determining what that HDE submission would look like. What sections would be included? How to present your data? And any other questions that come up from your review team before the HDE is submitted and that 75-day review clock starts. So if there's at all any questions about what your HDE should like and what should be included. We highly recommend the pre-submission process.

(Maria): Thank you.

Stephanie Shedd: Yes.

Coordinator: Once again, if you do have a question, please press Star 1 on your touchtone phone. The next question is coming from (Caroline McPherson). Your line is open.

(Caroline McPherson): Hi, sorry. My question was already answered. It was about use of off-label use of HDEs, but I actually do have a question on that same line. When the HDE is used off-label and there's no IRB approval for use of the

device, but it's used in an emergency situation, can you speak to your thoughts on that?

Josh Nipper: In those instances, we do ask that, I think it's the regulations even that we do ask that there is - that they do report back to the IRB and the sponsor within five days post-emergency use. You know, obviously we're not going to want to discourage the use in an emergency if that's in the best interest of the patient. But, you know, if there is no IRB and (unintelligible) no IRB approval at that point, we do ask that they notify the IRB and the company within five days.

The company is almost always going to know because if there's no IRB, you know, the physician has to get the device in some way. So they're usually in contact with the company for shipping and those kinds of things. So they, the company usually knows. But we do ask that the IRB be notified.

(Caroline McPherson): Okay and then billing in that scenario, I assume that something that would have to be discussed with the manufacturer?

Josh Nipper: I suppose. We don't typically get into the billing issues related to the devices.

(Caroline McPherson): Right.

Josh Nipper: So I don't know the best answer for you there.

(Caroline McPherson): Okay, thank you.

Coordinator: Once again, if you do have a question, please press Star 1 on your touchtone phone. And the next question is coming from (Carl Fisher). Your line is open.

(Carl Fisher): Hi, thank you. Could you please clarify on the comments regarding the expectation, the applicant change or intend to change the IFU in response to knowledge about an adverse event for off-label use? I may have misunderstood the response.

Stephanie Shedd: I'm sorry. So your question is changing an indication for use based on adverse events and things learned?

(Karl Fisher): I thought that I heard a previous answer to a question indicated that the manufacturer is expected to go forward changing the IFU when they become aware of an adverse event related to off-label use. I just wanted to clarify if I hear that correctly.

Stephanie Shedd: No, I mean just to clarify. I think that statement was if the manufacturer, sponsor is becoming aware of off-label use, then it's on them to consider making that marketing application for the off-label use. But it doesn't specifically have to be in response to adverse events or any other type of event.

(Karl Fisher): And just to clarify, that's a consideration not a requirement on the part of the manufacturer?

Stephanie Shedd: Right, it would be in their best interest to obtain approval for that use if it's becoming so prevalent off-label that it should be considered to be studied or marketed for on label use.

Josh Nipper: We have at least one high-profile example. I won't list it but, you know, if you go through the archives you could probably figure it out. There's at least one example where there was a series of HDE devices that were being used

off-label, you know, huge numbers of off-label use. That were - I'm not saying the use was inappropriate, but they were - the HDE was being off-label and there was no legally marketed device. And so there was some discussion with the company about restricting the device. Not restricting in the sense of a restriction, but limiting the device, you know, to only patient that really need to be HDE and not the off-label.

(Karl Fisher): Thank you.

Coordinator: And once again, if you do have a question, please press Star 1 on your touchtone phone. The next question is coming from (Ofisinia). Your line is open.

(Ofisinia): Hello, thank you. Could you please advise if there are guidelines for review timelines with HDE supplements for changes? It seems like the timelines are not the same as PMA supplements.

Stephanie Shedd: Yes, that's correct. A lot of the HDE supplements will have the same 75-day timeline, but it may be specific to the type of supplement. For example, if it's a 30-day notice type of supplement under the PMA supplement guidance, then I believe it still carries that 30-day review timeline under HDE. But it's going to kind of case specific depending on what kind of supplement is coming in. And your OHT or the Division of Submission Support, the email is there on your screen could advise on this specific case.

Josh Nipper: Most are 75 days, but then there is the 30-day notice provision that apply to HDE as well. So, you know, real-time supplements is only PMAs. They don't have 180-day supplement in real time and things like that. It's pretty much all 75 day.

(Ofisinia): Thank you.

Coordinator: At this time, we have no further questions. I will now turn the conference back to Ms. Aihie.

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 webpage at www.fda.gov/training/cdrhlearn by Tuesday, October 29. 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 today's webinar, please complete a short 13-questions 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. This concludes today's webinar.

Coordinator: This will conclude today's conference. All parties may disconnect at this time.

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