Module 3: Humanitarian Device Exemption (H-D-E) Program: Overview and Pre-approval Activities

Slide 1
Hello, my name is Donna Headlee. I am the Branch Chief of the Premarket Programs Branch, in the Division of Industry and Consumer Education. Welcome to CDRH Learn, CDRH's resource for multimedia industry education. The title of this presentation is, "Humanitarian Device Exemption Program -- Overview and Pre-approval Activities." The purpose of this presentation is to provide you with an overview of the Humanitarian Use Device and Humanitarian Device Exemption programs.

The acronyms for Humanitarian Use Device and Humanitarian Device Exemption are H-U-D and H-D-E, respectively, and I will be using these acronyms throughout this presentation. After watching this program, I hope that you will have a better understanding of the H-D-E program and the FDA's review process of an H-D-E application.

Slide 2
Let's review the learning objectives for this module. First, we'll define the terms H-D-E and H-U-D and learn how the programs are related. We'll discuss the approval threshold for an H-D-E, which is the determination of reasonable safety and probable benefit. We'll identify the contents of an H-D-E application and describe the review process.

Slide 3
We'll review the different types of actions that FDA takes after the review of an H-D-E. We'll go over the contents of an H-D-E approval package, and finally, we'll discuss some strategies and best practices for a successful H-D-E submission and review process.

Slide 4
Let's now discuss the rationale for the HDE Program.

The diagnosis of a rare disease or condition can be a devastating occurrence for the patient and their family. Only a portion of the 7,000 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 meet the FDA standard of reasonable assurance of safety and effectiveness. As a result, it was uncommon for medical devices for rare diseases or conditions to be legally marketed in the United States.

In order to address this challenge, Congress passed a provision in the Safe Medical Devices Act of 1990. The Law created a new regulatory pathway for products intended for rare diseases or conditions. This is the HDE Program.

Slide 5
Let's discuss the actual definitions of an H-U-D and H-D-E as defined in the Federal Laws and Regulations.

An H-U-D is a medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in not more than 8,000 individuals in the United States per year.

Slide 6
From Section 520(M) of the Federal Food, Drug, and Cosmetic Act (or FD&C Act), an H-D-E is a marketing application for an H-U-D. An H-D-E is exempt from the effectiveness requirements of Sections 514 and 515 of the FD&C Act, and it's subject to certain profit and use restrictions.

Slide 7
Getting an H-D-E to market involves a two-step process.

First, an applicant must obtain an H-U-D designation from the FDA's Office of Orphan Products - referred to as OOPD.

After the device is designated as an H-U-D, the applicant then submits the H-D-E application to the proper FDA Review Center: either the Center for Devices and Radiological Health (CDRH) or the Center for Biologics Evaluation and Research (CBER) - depending on which Center regulates the device.

Slide 8
A device is eligible for review in an H-D-E application if it meets two criteria:

First, OOPD must designate the device as an H-U-D. And second, there cannot be a legally marketed device for the same disease or condition granted under another regulatory pathway, that is, premarket notification, premarket approval, or de novo.

Slide 9
The approval threshold for an H-D-E is based on two factors:

The first is 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 burden is the same for both PMA and H-D-E devices. Reasonable assurance of safety consists of <u>not</u> 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, require demonstration of probable benefit. This difference in determination of effectiveness is the key differences between PMA and H-D-E devices.

Slide 10
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.

Slide 11
In this next section, I am going to discuss the contents of an H-D-E application.

Slide 12
The H-D-E application should contain a copy of, or reference to, the H-U-D designation letter granted by OOPD.

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 a discussion of all device components and accessories and how they work; design drawings and specifications; and a listing of the materials of use.

Slide 13
The application should include a statement of the proposed indications for use. This should be consistent with the H-U-D designated disease or condition referenced in OOPD's H-U-D 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/or clinical evidence. As a conclusion summary of this valid scientific evidence, the applicant should explain why the probable benefit outweighs the risk of use of the device.

Slide 14
The H-D-E application should also contain manufacturing information. Note that the device must comply with the Quality System Regulation reference in 21 CFR Part 820.

The sponsor should document the amount of money to be charged, and if requesting to make a profit, the sponsor should request an exception to the profit prohibition.

And finally, the application should include the physician labeling and, if applicable, the patient labeling.

Slide 15
The labeling for an H-D-E must contain a statement that the device is a humanitarian use device and that, although the device is authorized by Federal Law, the effectiveness of the device for the specific indication has not been demonstrated.

Slide 16
The H-D-E application should also contain All applicable clinical evidence. Clinical evidence may come from various sources, including clinical studies subject to Investigational Device Exemptions (IDEs) -that is- studies conducted in United States, Outside of the United States experience, and literature analyses. This should be provided whether the information is adverse or supportive.

Slide 17
Preferably, the clinical evidence submitted in the H-D-E should include summaries, conclusions, and results of all clinical experience or investigations. The information should include evidence that supports both the safety and probable benefit.

Slide 18
We recognize that there are limitations and challenges in the collection of relevant clinical evidence for an H-D-E device.

Because H-D-Es are limited to patient populations with a rare disease or condition, it may be challenging to find and recruit these patients into a clinical study, this may lead to smaller sample sizes in a prospective clinical study.

And second, because there is no available comparable device for the same indication, these studies may often lack an active control arm and/or randomization.

Slide 19
In the next section of this module, I am going to discuss FDA's review process of an H-D-E application.

Slide 20
Sometimes visualizing something in a diagraph assists in clarifying the process. The next couple of slides show a flow chart, identifying key milestones in the submission and review process. I'll walk you through this diagram to show the

overview of the process, and then we'll go into more specific detail about the key milestones of this process.

The Blue Ovals indicate the key milestones, FDA actions and activities that take place. The Diamonds illustrate the day, by which, the FDA will take action for the key milestone.

Starting from the top left of this screen, we begin with Granting the H-U-D Designation, then receipt of the H-D-E Submission. We then proceed with the Filing Review and then the Substantive Review.

Slide 21
During the substantive review process, the FDA may seek input from an advisory committee.

After the substantive review is completed, FDA will issue an Action. Available actions, in order of most favorable to least, are: approval, approvable pending deficiencies, major deficiency, and not approvable.

Slide 22
Upon receipt of the HDE, the FDA Review Process starts with the formation of the FDA Review Team. This consists of a multi-disciplinary team of individuals with specific expertise needed to evaluate the application. A typical team may include between 5 and 15 individuals and will often have backgrounds listed on this slide.

Slide 23
Now let's discuss some of the key milestones in more detail. We start with the filing review. This review is a threshold determination that the application is sufficiently complete to proceed with the full review. Please note, this is <u>not an in-depth review</u> to determine approvability.

The FDA will notify the applicant of the Filing or not Filing Decision within 30 calendar days. If the submission is not filed, the FDA will identify what is needed in order to file the application.

Slide 24
There are several reasons why an H-D-E may not be filed. The application is incomplete, in that it does not contain all the information required under 21 CFR 814.104(b).

The application lacks a statement of either financial certification or disclosure, in accordance with 21 CFR Part 54.

FDA determines there is a legally marketed device for the same disease or condition granted under 510(k), PMA, or de novo to treat or diagnose the disease or condition for which approval of the H-U-D is being sought; and/or.

The application contains an untrue statement of material fact or omits material information.

Slide 25
Once the application is filed, the FDA Review Team begins the Substantive Review of the submission. This will consists of the in-depth scientific, regulatory and quality systems reviews.

During the Substantive Review, FDA may interact with the applicant to address and resolve deficiencies found during the reviews. These tend to be deficiencies that are possible to address during the review cycle. The purpose is to allow the review to continue with the goal of trying to reach a final decision within the review milestones. Note that the FDA Review Clock continues throughout this phase and does not stop.

Slide 26
I mentioned earlier that the FDA may choose to take an H-D-E submission to an Advisory Committee Meeting. Let's review what's involved with that process now.

The FDA Advisory Committee consists of an independent panel of special government employees with expertise relevant to the topic. The individuals come from a variety of backgrounds and the committee is usually composed of expert clinicians, statisticians, an industry representative and a patient representative. The meeting of the Committee is open to the public.

Slide 27
FDA may seek input from an Advisory Committee for a number of reasons. For example, the the device may feature a novel technology that has the potential to significantly impact clinical practice.

The valid scientific evidence may provide significant uncertainty, as to whether the probable benefit of the device outweighs its probable risk, and thus, FDA would benefit from the input from an independent outside body of experts.

The application presents unanticipated serious safety concerns, or other issues where input may help with FDA's review, such as missing data or protocol deviations.

Slide 28
At the conclusion of its review, the Advisory Committee will provide a recommendation to the FDA. The Committee will weigh in on the safety and probable benefit profile of the device, whether the benefits outweigh the risks, conditions of approval, and labeling.

Slide 29
In this next section, I am going to discuss FDA actions for an H-D-E application.

Slide 30
At the end of the Substantive Review of the H-D-E application, FDA will make a decision and take an Action. Let's review these options in detail.

The decision that all sponsors hope to achieve is approval. If FDA issues an Approval Order, the device is legally marketed. The approval order lists the approved indication for use and any conditions of approval. This is the only action in which the device is legally marketed.

If the application is close to approval but there are minor deficiencies, the FDA will issue an Action of Approvable Pending Deficiencies. The device is not legally marketed. The FDA letter will identify deficiencies that need to be resolved in order for the application to be approved. Common reasons for an approvable pending deficiencies letter include: unresolved labeling or lack of resolution of the post-approval study design, if one was required. Or, FDA has not determined that the manufacturing facilities, methods and controls are in compliance with the Quality System Regulation.

Slide 31
A third action that the FDA may take is to issue a Major Deficiency Letter. In this case, the device is not legally marketed. This letter will identify deficiencies that need to be resolved. But unlike the Approvable Pending Deficiencies action, FDA believes that these deficiencies cannot be adequately resolved interactively.

And finally, the FDA may issue a Not Approvable Letter. In this case, the device is not legally marketed. This letter will identify significant deficiencies that need to be resolved. And in contrast to the Major Deficiency Letter, the FDA believes that new clinical and/or substantive preclinical evidence will need to be collected.

Slide 32
Now that we've reviewed the various actions the FDA may take, let's discuss what happens when an HDE is approved.

Slide 33
Transparency in FDA's activities and decision-making allows the public to better understand the FDA's decisions and assists in providing information for health care providers and patients. To facilitate transparency, the FDA generates and publishes several key documents regarding the H-D-E. These are the H-D-E Approval Order and the Summary of Safety and Probable Benefit, or S-S-P-B. We'll review each of these documents over the next few slides.

The approval package will also contain the approved labeling, which will consist of professional labeling and may include patient labeling. And finally, the FDA

will prepare Consumer information, which is a short, plain-language summary of the device and its intended use.

Slide 34
Perhaps the most important document is the HDE Approval Order. This is the letter that informs the applicant the H-D-E is approved. The Order identifies the H-D-E number and H-U-D number. Note that these are two different numbers.

The order will also outline the conditions of approval, any post-approval requirements, and any specific items unique to the H-D-E, such as the annual distribution number, specific reporting requirements, or post-approval studies.

Slide 35
The conditions of approval may include items such as use of the approved labeling, post-approval record-keeping requirements, and submission of H-D-E supplements for changes

Slide 36
Other conditions include: mandatory reporting, including periodic, or annual reports; as well as medical device reports, or MDRs, and product recalls.

And finally, other conditions include the conduct of post-approval studies and the requirement to provide updates to clinicians.

Slide 37
We've talked about post-approval studies as one type of condition of approval.

There are some reasons why the FDA may require that a post-approval study be conducted. We may need to better understand the long-term performance of the device. This is more likely for a permanent implant whose performance will likely exceed what was studied in the H-D-E application.

FDA may wish to further evaluate the device or component performance, and/or evaluate the learning curve for use of the device that may require the need for improved training on the use of the device.

It should be noted that FDA and the H-D-E Applicant must agree on the post-approval study, either in full, or, more commonly, in a sufficient detail, in order for FDA to approve the H-D-E.

Slide 38
The SSPB is a document prepared by the FDA. It consists of a summary of the information included in the H-D-E submission and explains the basis for FDA's approval of the H-D-E and the applicant's demonstration that the device is reasonably safe and showed probable benefit. This document contains

information such as the device description, preclinical information, clinical information, and summary of the Advisory Committee Meeting if one was held.

Slide 39
Even though the H-D-E is approved, there are some limitations. First, IRB approval is required before the H-D-E-approved device may be used at the institution. Note that approval is required for the site, and not for each patient.

The only exception to this is if the H-D-E device is used in an emergency situation. We address this topic in the CDRH Learn module on H-D-E Program: Post-approval Activities.

Importantly, please check your IRB's policies and procedures for specific requirements.

Slide 40
Another limitation of H-D-E approval is with the approved labeling. The device labeling must clearly identify the device as an H-U-D. It must state that the effectiveness for that indication has not been demonstrated. The labeling must identify the pediatric population if the H-D-E was approved for a specific pediatric indication.

And finally, the H-D-E may not be sold for profit. There is an exception to this, which we'll discuss in a different module.

Slide 41
There are several excellent resources on the FDA website for information on H-D-Es.

This slide lists the U-R-L that will take you to a table that lists the H-D-Es approved by CDRH. I've also included a screenshot of this home page. The database lists the H-D-E Number, the device name, the company name, as well as the device description and device indications.

Slide 42
On this next slide, we have the screenshot and U-R-L for the HDE Database. This is a publically-available database that lists information on all H-D-Es approved by both CDRH and CBER.

Slide 43
I'd like to conclude with some strategies for a successful submission: Be organized, Be prepared, and Be responsive.

Slide 44
First: Be organized.

Submitting a well-organized, administratively and scientifically complete submission can assist in the review process. An application should have a comprehensive Table of Contents, detailed sections, include all test reports, graphs/tables that are clearly labeled, and consecutive page numbers.

Slide 45
Second: Be Prepared

Have your team ready to answer questions. Have copies of the HDE submission and any other submissions or interactions you've had with the FDA, such as Pre-Submissions,

And, be ready for manufacturing and bioresearch monitoring (BIMO) inspections.

Slide 46
And finally: Be responsive.

Make sure we know how to get in touch with you. Provide your complete and accurate contact information, including your name, email address, phone number, and fax number. Please double check the contact information, as an incorrect email address can lead to difficulties in communicating. We suggest you provide a backup or alternate contact for you. And if you are a foreign applicant, please list a United States representative who is available to assist with timely communication.

Answer all of the FDA questions and deficiencies when you say you will. If you do not understand a deficiency or the FDA's request, please contact the FDA Lead Reviewer as soon as possible.

Be in touch. Discuss questions, concerns with the lead reviewer and have your subject matter experts available for consult when needed.

Slide 47
Be ready to interact on labeling, especially toward the end of the FDA's review, have your decision-makers available for a quick turnaround.

And finally, develop a good post-approval study proposal and work interactively with the FDA Review Team to finalize a scientifically-sound study that may be approved.

Slide 48
After watching this program, I hope that you will have a better understanding of the H-U-D and H-D-E programs.

In conclusion, let's summarize key points of this module.

First, an approved H-D-E authorizes an applicant to market an H-U-D. Second, the basis for H-D-E approval is: reasonable assurance of safety and probable benefit. Third, an H-D-E application consists of information describing the device, and valid scientific evidence to support reasonable safety and probable benefit.

Slide 49
The FDA website contains useful information on the H-D-E program and approved H-D-Es.

Next, the HDE Review Process involves several key decision points and features interaction between FDA and the applicant to help complete the review.

Slide 50
Next, the H-D-E approval package contains the approval order outlining the conditions of approval, the labeling, the SSPB, and consumer information. And finally, a well-organized, complete application will assist both the applicant and the FDA with the review process.

Slide 51
The next few slides provide some additional resources and guidance documents for the H-D-E/ H-U-D programs.

Slide 52
Pause to allow them to read - 1. 2.3.

Slide 53
CDRH provides multiple opportunities for industry education.

CDRH Learn is an innovative educational tool, which consists of learning modules describing many aspects of medical device and radiation emitting product regulations, covering both premarket and postmarket topics. Modules are provided in various formats, including videos, audio recordings, and slide presentations.

Device Advice is a text-based resource that explains many aspects of medical device laws, regulations, guidances, and policies, covering both premarket and postmarket topics.

In addition, the Division of Industry and Consumer Education (D-I-C-E) answer's questions (by phone and email) from industry and consumers related to medical devices. For additional information on these or any other medical device regulatory topics, feel free to contact D-I-C-E.

The web links and contact information to these resources are provided on this slide.

Thank you for watching "Humanitarian Device Exemption (HDE): Overview and Pre-approval Activities. For further information, please consider watching the additional modules on the H-U-D and H-D-E programs in CDRH Learn.

Thank you for your attention.