Module 4 Humanitarian Device Exemption (H-D-E):
Postapproval 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, in the Office of Communication and Education. Welcome to CDRH Learn, CDRH's resource for multimedia industry education. The title of this presentation is "Humanitarian Device Exemption - Post-approval Activities."

During this presentation, I'll be referring to two phrases that have similar names and acronyms. One is Humanitarian Use Device or H-U-D and the other is Humanitarian Device Exemption, abbreviated as H-D-E. As you follow along, make sure to pay careful attention to which program is being discussed.

Slide 2
Let's review the learning objectives for this module.

First, we'll review the regulatory responsibilities for an approved H-D-E. We'll discuss the post-approval reporting requirements for an H-D-E. Next, we'll learn about the purpose of the annual incidence reassessment.

Slide 3
We'll review the different types of H-D-E Supplements. And finally, we'll discuss the role of the Pediatric Advisory Committee and Institutional Review Boards, or IRBs, as they pertain to approved H-D-Es.

Slide 4
On this slide, I've listed the post-approval requirements that pertain to H-D-Es and the corresponding regulation. These requirements may be categorized into those specific to H-D-Es, and those that pertain to all medical devices.

The HDE-specific requirements are: H-D-E Supplements, IRB approval, and H-D-E periodic reports. The general requirements are: Medical Device Reporting, also referred to as MDR, and Recalls.

Slide 5
In the next section, I am going to discuss the Responsibilities of H-D-E- Holders and IRBs for approved H-U-Ds.

Slide 6
The H-D-E holder must ensure that the H-U-D is used only in facilities with functioning IRBs.

Slide 7

The holder of an H-D-E must maintain specific records for the H-D-E. In accordance with 814.126(b)(2), H-D-E holders must maintain records of the names and addresses to which the H-U-D was shipped, correspondence with reviewing IRBs, as well as any other information requested by FDA or the reviewing IRB.

Slide 8
IRBs must have certain policies in place for the approval and continuing review of an H-U-D. The IRB may require informed consent before an H-U-D is used. IRBs may give a blanket approval for a particular H-U-D at an institution, or may approve the use of an H-U-D on a case-by-case basis.

Slide 9
A question that the FDA often receives is: can a physician use an H-U-D device if IRB approval for use on the patient has not been obtained and if a blanket approval has not been granted?

The answer is: yes, if the situation is an emergency.

If a physician determines that IRB approval for the use of the H-U-D at the facility cannot be obtained in time to prevent serious harm or death to the patient, then the H-U-D may be used without prior IRB approval.

In this case, the physician must provide a report to the IRB chair within 5 days of the emergency use. The report must include written notification of the use of the device, identification of the patient involved, the date on which the device was used, and the reason for use.

These requirements are outlined in 21 CFR 814.124(A).

Slide 10
Because the FDA has made a determination of safety and probable benefit for use of the H-U-D only within its approved indications, FDA recommends the treating physician do several things if the device is used in an emergency. The physician should obtain informed consent from the patient, should check with the IRB for any applicable policies, should maintain patient protection measures, and should submit a follow-up report to the HDE holder.

Slide 11
There are two scenarios for use of an H-U-D for research purposes: one - on label and, two - off label. Let's discuss each of these scenarios.

As long as the H-U-D is used in accordance with its approved indication for use under the H-D-E, the FDA considers the study exempt from the Investigational Device Exemption, or IDE, regulation. However, as required for all FDA-regulated clinical studies, the requirements for IRB review and approval and protection of human subjects do apply.

If an H-U-D is used off-label, that is, for an indication other than what was approved under the H-D-E, and the physician is collecting safety and/or probable benefit evidence, the investigator needs to comply with the IDE regulation. The requirements for IRB review and approval and protection of human subjects also apply.

Slide 12
In accordance with the FDA regulations, there are post-approval reporting requirements. An H-D-E holder needs to submit termination or with-draw-al of IRB approval reports, periodic reports, which are often referred to as annual reports, and, post-approval study reports, if a post-approval study was mandated.

Slide 13
If an IRB withdraws its approval of use of an H-U-D, the holder of the H-D-E must notify the FDA within 5 working days after being notified of the withdrawal of approval.

Slide 14
After an HDE is approved, it is possible for the FDA to approve a comparable device with the same indication under the traditional marketing authority, that is, a premarket approval application, or PMA, premarket notification, or 510(k), or de novo. In these situations, the comparable device would have demonstrated reasonable assurance of effectiveness, which, as we've learned, is a higher evidence bar than what is required for an HDE, which is probable benefit.

As a result, the H-U-D no longer meets an unmet need, and specifically, the requirements of 520(m)(2)(B) of the FD&C Act. In this case, the FDA will withdraw approval of the H-D-E.

Slide 15
Over the next few slides, I am going to discuss the Regulatory Requirements for Periodic Reports in more detail. Periodic reports are often referred to as annual reports.

An H-D-E holder is required to submit Periodic reports. By default, this is required annually unless FDA has required reports to be submitted more frequently. The reporting timeframe is identified in the approval order.

The periodic report should account for the devices used, including the number of devices shipped or sold since H-D-E approval in the calendar year. The report should account for multiple devices used in the same patient, and if a device is used on multiple patients.

The report should provide an update on the clinical experience of the device. This should include safety information, medical device reports, or MDRs, data

generated from postmarket studies, and any information, that may affect the contraindications, warnings, precautions, and adverse reactions identified in the device's labeling.

The report should also include a summary of the supplemental changes made to the device. We will discuss H-D-E supplements later in this module.

Slide 16
The periodic report should include updated information on the H-U-D and H-D-E Status. This includes the justification for the H-D-E, which should explain why the device would not otherwise be available, a statement that no comparable device, other than another H-U-D approved device, or a device being studied under an approved IDE, is available to treat or diagnose the disease or condition.

The report should explain why the probable benefit outweighs the risk of use of the H-U-D, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment, and, finally, the report should include the annual incidence reassessment.

Slide 17
The annual incidence reassessment, or A-I-R, is an annual update of the patient population estimate for the current U.S. population. This ensures that the H-U-D continues to qualify through the H-U-D/H-D-E pathway.

If the patient population estimate exceeds 8000 as a result of the A-I-R, the HDE may become ineligible for the HUD/HDE pathway. Some options for the H-D-E may include: withdrawal, conversion to a treatment IDE, and the H-D-E holder working to identify a new H-U-D or orphan subset.

Slide 18
If the cost of the device exceeds 250 dollars, the H-D-E holder must report an assessment completed by an independent Certified Public Accountant or a responsible individual of the company, verifying that the amount charged does not exceed the costs of research, development, fabrication, and distribution. If the device cost does not exceed 250 dollars, the justification requirement is waived.

Slide 19
Additional reports that are not specific to the H-D-E program but, are required for all marketed devices include: MDR reports and recall notifications. In addition, if a post approval study is mandated - post-approval study reports should be submitted, as outlined in the approval order. For further information related to these reporting requirements, please refer to the specific sections in Device Advice and CDRH Learn.

Slide 20

The manufacturer of an approved HUD has some reporting responsibilities. Per 21 CFR 803, the manufacturer must report H-U-D-related deaths, serious injuries, or malfunctions within 30 calendar days. This is based on information they may receive or otherwise become aware of, from any source, which reasonably suggests that the HUD: (1) may have caused or contributed to a death or serious injury, or (2), malfunctioned, and the malfunction of the device would be likely to cause or contribute to a death or serious injury if the malfunction were to re-occur.

Slide 21
H-D-E supplements are addressed under 21 CFR 814.108 - Supplemental applications under Subpart H in the H-U-D Regulation and also addressed under 21 CFR 814.39 - PMA Supplements under Subpart B of the PMA Regulation.

Slide 22
Throughout the lifecycle of a medical device, modifications to the device are often needed. Modifications that affect the safety and probable benefit of the device require the FDA's review and approval of an H-D-E supplement. Types of supplements for H-D-Es are: a 75-Day Supplement, a 30-Day Notice and a Special H-D-E Supplement Changes Being Effected.

The type of H-D-E supplement required depends on the evidence needed to demonstrate the safety and probable benefit of the change. I am going to discuss each of these in more detail over the next few slides.

Slide 23
Let's begin with the most common type of H-D-E supplement: The 75-day supplement. This type of supplement includes changes that consist of Device modifications/Design changes, Labeling changes, Manufacturing or Sterilization Site changes, Post-Approval Study Protocol changes, requests for an annual distribution number, or ADN, profit eligibility or modification to the ADN.

Some examples of changes that could meet the criteria of a 75-Day Supplement include: a change in device materials, a hardware or software modification, or a request to extend the shelf-life of the device.

Slide 24
The next type of supplement is a 30-Day notice. 30-Day notices should be submitted for modifications to the manufacturing process. If the FDA review determines that the submission does not qualify for a 30-day notice, FDA will convert the submission to a 75-day supplement. Some examples of changes that could meet the criteria for a 30-day Notice includes: converting a process from manual to automated, obtaining new manufacturing equipment, or using an alternate supplier.

Slide 25

A Special H-D-E Supplement - Changes being Effected - should be submitted for specific types of labeling and manufacturing changes that enhance the safety of the device.

For labeling changes, this usually involves newly acquired safety-related information not previously submitted to the FDA; and where the information triggers a labeling change that adds or strengthens a contraindication, warning, or precaution.

Qualifying manufacturing changes are those that enhance safety but do not impact probable benefit. Generally, they are changes that add a step to the quality control or manufacturing processes.

Slide 26
Unlike other supplements, changes that qualify for a Special H-D-E Supplement - Changes Being Effected - can be implemented prior to FDA approval. Please note, there is a 30 day review clock for these types of changes.

An example of a labeling change is: Improve the instructions for use- such as a clarification or addition of an adverse effect.

An example of a manufacturing change is the addition of a new quality assurance inspection step.

Slide 27
One type of change I want to clarify is, that if an H-D-E holder wants to request a new or expanded indication for use, outside of the existing H-U-D designation, this CANNOT be submitted as an H-D-E supplement. A new H-U-D designation application would need to be submitted to the Office of Orphan Products Development, or OOPD.

Slide 28
CDRH works closely with the Office of Pediatric Therapeutics -to facilitate review of certain H-D-Es by the Pediatric Advisory Committee, or the PAC. The PAC conducts periodic annual reviews of approved H-U-Ds labeled for pediatric patients and allowed to make profit. They review the devices to ensure that the H-U-D remains appropriate for the pediatric populations for which it is approved. FDA's Office of Pediatric Therapeutics, in FDA's Office of the Commissioner coordinates this review.

Slide 29
Information presented to the PAC includes: MDRs received since approval and relevant safety information, a summary of any post-approval studies, and a summary of relevant peer-reviewed literature published since approval.

The Review Questions focus on whether the probable benefit/risk profile of the device for the pediatric population continues to support the H-D-E for which the exemption was granted. You can find further information related to the PAC at the website identified on this slide.

Slide 30
Let's recap the key points we covered in this module. First, a sponsor has a number of regulatory responsibilities after an H-D-E is approved, and for updating the FDA on changes to the device. Second, there are post-approval reporting requirements after an H-D-E is approved. Next, the annual incidence reassessment is an annual estimate of the target population with the disease or condition, which is used to ensure that the device continues to qualify through the H-U-D/H-D-E pathway.

Slide 31
Modifications that affect the safety and probable benefit of the device require the FDA's review and approval of an H-D-E Supplement. And finally, organizations such as the Pediatric Advisory Committee and Institutional Review Boards have specific roles for H-D-E-approved devices.

Slide 32
The next few slides provide some additional resources and guidance documents for the
H-D-E/ H-U-D programs.

Slide 33
I encourage you to review them if you have any questions about H-U-Ds and H-D-Es.

Slide 34
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) answers 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 Post Market 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.