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Hello, my name is Katie Chowdhury. I'm a Biomedical Engineer/Health Science Administrator in the Office of Orphan Products Development. Welcome to CDRH Learn, the Center's resource for multimedia industry education. This presentation will provide stakeholders with comprehensive, interactive, and easily accessible information on Humanitarian Use Device and the Humanitarian Device Exemption programs.

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After watching this presentation, I hope that you'll have a better understanding of the Humanitarian Use Devices designation and Humanitarian Device Exemption programs, and why Congress established them. The acronyms for these terms are HUD and HDE, respectively, and I'll be using each of them throughout the presentation. Even though the acronyms look similar, they are two very distinct programs. This presentation today focuses on aspects related to the HUD program.

I'll also define the term 'population estimate' which is important to the HUD designation program, and I'll explain how this term may be different for treatment and diagnostic devices. You'll learn how HUDs apply to pediatric patients and, finally, we'll review where to submit a HUD application.

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There's a two-step process if a Sponsor wishes to get their device commercialized in the United States through the HUD/HDE marketing pathway. First, a Sponsor submits a HUD designation request and receives approval from the Office of Orphan Products Development, or OOPD. Second, once the HUD designation is granted, the Sponsor submits the HDE marketing application to the Center for Devices and Radiological Health or to the Center for Biologics Evaluation and Research, whichever Center is responsible for the review of that medical device. We'll cover Step One of this process in this presentation. Step Two is covered in another CDRH Learn module on HDEs.

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Now let's discuss the Humanitarian Use Device, or HUD, program in more detail.

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In 1990, Congress established the HUD designation and HDE marketing pathway program. This program was created to encourage the development of devices for

rare diseases or conditions. Congress recognized that the small market could create an economic disincentive for device development for rare diseases. Traditionally, in order for a device to enter the market in the U.S., there had to be a reasonable assurance that the device was safe and effective. Under the HUD/HDE pathway, the Sponsor is exempt from having to demonstrate device effectiveness, and needs to demonstrate that 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.

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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 8,000 individuals per year in the United States. The incidence limit was raised from 4 to 8 thousand with the passage of the 21st Century Cures Act. It is important to note that the definition outlined in Title 21 of the Code of Federal Regulations, or CFR, under Section 814.3(N), is currently being updated to coincide with the Law.

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OOPD has a published Guidance document that may serve as a reference for Sponsors and FDA staff on the HUD Program. It can be found at the link on this slide. We encourage you to read the HUD Guidance for additional information about the program and details regarding the content of the HUD designation request.

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Step One of the process is for the Sponsor to submit a HUD request to OOPD. The submission must include two copies. One must be a hard copy, the original, and the second may be either a hard copy or an electronic copy, also known as an eCopy. I'll cover where to submit this information later in this presentation. Once OOPD receives the HUD request, the Office sends the Sponsor an acknowledgement letter with an assigned HUD number for each application.

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Let's now discuss the content of the HUD request that the Sponsor sends to OOPD. The request should contain a cover letter. This should request that OOPD consider the device for 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 provide a proposed population estimate. This is a calculation of the number of patients affected or manifested with the disease or condition, in the U. S., per year. The request should tell us about the device and how it would be used. This should include a written description of the device, including engineering

diagrams, as well as the scientific rationale supporting the use of the device. Please include all relevant preclinical, clinical, and/or proof-of-principle data pertaining to the device.

Finally, the request should include supporting documentation, with applicable references, demonstrating that the device is designed to treat or diagnose a rare disease or condition, or orphan subset, that occurs in not more than 8,000 individuals per year in the United States.

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OOPD reviews each request in a specific, consistent manner. First, we evaluate the disease or condition that the 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. Note that we may broaden the requested designation, if we determine the device may be used to treat or diagnose more people with that disease or condition. The caveat here is that the entire population with the disease or condition must be not more than 8,000 individuals per year. If the target population is over 8,000, a sponsor may still obtain a HUD designation if they can explain why the device is limited to an orphan subset. We'll address orphan subsets later. OOPD reviews the HUD designation request within 45 calendar days and issues the Sponsor a decision letter.

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OOPD may approve, disapprove, or request additional information. Approval means that the device is designated for a disease or condition that occurs in not more than 8,000 patients per year. Some designations may be broader. We disapprove a designation if we determine that the population exceeds 8,000 patients per year. And finally, we may request additional information if needed to make a final decision.

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How does OOPD evaluate whether a device treats or diagnoses a rare disease or condition? We'll review how the device works to treat or diagnose the disease and how it performs in the patient population. For example, an artificial heart will pump blood to the body in patients with heart failure. OOPD also considers other factors about the disease such as pathogenesis, course of the disease, prognosis or resistance to treatment. OOPD designates a device for a disease and not for a specific indication or proposed label for the device. Our FDA colleagues in CDRH or CBER determine the final labeling for the device during their review of the HDE marketing application. Sometimes our designations are broader than what the Sponsor requested and what winds up as the HDE-approved indications for use.

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As we discuss the HUD designation, it's important to understand the difference between disease prevalence and disease incidence. Prevalence is the total number of patients with a disease or condition at a given time. As an example, this is the number of patients with Cystic Fibrosis on April 1, 2015. In contrast, Incidence is the number of new patients diagnosed with a disease or condition during a particular time period. Unlike prevalence, this would be the number of NEW patients diagnosed with Cystic Fibrosis from January 1 to December 31, 2015.

FDA generally relies on incidence, and not prevalence, to determine if a device qualifies for a HUD.

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A population estimate is used to determine if a device can qualify as a HUD. For therapeutic devices, the population estimate needed for a HUD designation is generally the number of new patients per year diagnosed with the relevant disease or condition, and potentially eligible for treatment with the device. In order for a device to receive a HUD designation, this number must be not more than 8,000 patients per year, in the U.S.

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For diagnostic devices, the population estimate is different. The estimate for diagnostics is the number of new patients per year who would be subjected to the device, regardless of the test result and the patient's medical status. As a result, it's possible for a diagnostic device to not qualify for a HUD designation, even if it's intended to diagnose a rare disease or condition.

Why is that? A diagnostic device may be used on a larger number of people who have symptoms of the disease or condition, and this number may exceed the 8,000 individual limit. After use of the device, we may find that not more than 8,000 individuals actually have the disease or condition. But again, the population estimate for diagnostics is based on the number of patients on whom the device would be used. Let me illustrate this with an example. Let's assume that we have a diagnostic device that's used to screen newborns for a rare disease or condition. This device would be used on all newborns. The number of newborns in the U.S. is well over three million. Because this number far exceeds 8,000, the population estimate for this diagnostic would disqualify the device as a HUD.

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There are certain circumstances where a patient may need to use a device more than once a year to treat his or her disease or condition. In these cases, the population estimate depends on the total number of new patients who would be eligible for, or subjected to, the device in a given year, and not the total number of expected uses of the device. Let's take the example of a device that treats both eyes of a patient, AND where each eye is treated on a different day, in the same year. For purposes of the population estimate, we would count this as one patient, and not two, because the population estimate is based upon the patient, and not total number of uses.

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There are cases where the target population exceeds the 8,000 limit and is therefore not eligible for the HUD/HDE marketing pathway. It's possible for the Sponsor to still qualify for a HUD if the device meets the criteria of an "Orphan Subset." An orphan subset is a population of individuals with a non-rare disease, where both the device is appropriate for use, AND, use of the device on other individuals with the disease is inappropriate because of some feature of the device. These features include, but are not limited to, the size of the device, mode of action, or risk profile. An orphan subset cannot be considered without reference to the device, specifically, to the property or properties that render the device medically or scientifically inappropriate to use outside of the subset of interest with the non-rare disease or condition.

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Based on the definition of an orphan subset, OOPD considers some factors during a HUD designation review to determine whether an appropriate orphan subset exists. We'll review the adverse event profile of the device. If the device is shown to have a serious risk, it could be restricted to some patients.

We'll also review the mechanism of action and factors such as whether the device characteristics, like size, may limit use of the device. For example, a large blood pump may be too large to fit in the chest cavity of a small person. And finally, we'll review all prior clinical experience. This information may show that the device has no significant activity in some patients, and thus, should only be used in the remaining population with the disease.

The Sponsor may submit all relevant evidence in the application to justify the orphan subset population if it is being requested.

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In contrast, there are a number of factors that the Office does not consider when evaluating an orphan subset for a non-rare disease. First, there are clinical trial

exclusions. A specific patient subgroup that isn't being studied in a proposed clinical trial, should not categorically be excluded from the population estimate if there's no scientific or medical reason to preclude use of the device to those patients.

That being said, the 2nd factor we don't consider is if a Sponsor requests to have a narrow indications for use for the device if there's no scientific reason to limit use to those patients.

Third, an unmet medical need does not automatically constitute an orphan subset. Also, standard of care is not a factor that's considered, since it can evolve with the study of new treatment options - and, it may be determined, at some point, that the device is now the standard of care and is appropriate to be used in the larger patient population. And finally, the Office does not consider the price of the device when determining an orphan subset during our review.

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OOPD reviews the device description and scientific rationale in order to understand how the device functions, and what disease or condition the device may treat or diagnose. The scientific rationale supporting use of the device for the rare disease or condition, or orphan subset of a non-rare disease or condition, should contain all relevant preclinical, clinical, and/or proof-of-principle data pertaining to the device as applicable - whether positive, negative, or inconclusive. This information can also be used to support an 'orphan subset' claim in the application as discussed earlier. It should be noted that the preclinical information about whether a device has been verified and validated against the proposed device design specifications is reviewed in the HDE marketing application that's submitted to CDRH or CBER, and not in the HUD request.

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For the purpose of a HUD request, the pediatric population is defined as those younger than 22 years of age. In general, we'll designate for the entire population, both pediatric and adult, if the population estimate of the disease or condition affects or is manifested in not more than 8,000 patients per year in the United States. If the overall population exceeds 8,000, a sponsor may pursue a pediatric population if that is less than 8,000.

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HUD designation requests are submitted to the Office of Orphan Products Development at the FDA headquarters. The address is provided on this slide.

Remember to submit a signed and dated original, hard copy, and a 2nd copy that can be either paper or an eCopy.

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Please contact our Office if you have any questions regarding the HUD program. Our email and phone number is provided on the slide.

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Additional assistance regarding the HUD program may be obtained from the OOPD website or from the HUD guidance. The links are provided on this slide for your reference.

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Let's recap the main points of this module.

A HUD designation allows for a device, intended for use in not more than 8,000 patients per year with a rare disease or condition, to be eligible for an alternative pathway to market. The HUD/HDE marketing pathway is a two-step process. Step One is the Sponsor's submission of the HUD designation request AND review and approval by the Office of Orphan Products Development. We covered Step One in this module. Another module addresses Step Two. We reviewed what should be included in your HUD Request.

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OOPD designates devices for a disease or condition and not for a specific indication or label.

We defined disease incidence and introduced the concept of the population estimate in various scenarios. These are important in determining whether a device is eligible for a HUD.

And finally, where appropriate, a device for a non-rare disease or condition may qualify for an orphan subset if the population estimate is fewer than 8,000 patients per year.

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Thank you for watching this presentation. Please consider watching the entirety of the HUD and HDE program modules to develop a complete understanding of these programs.

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Thank you for your attention.