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Humanitarian Use Devices

Context

Humanitarian Use Devices (HUD) are medical devices developed to address challenges faced by a very small number of patients, and for which no expectation of recovering development/manufacturing costs can be considered if a traditional market size risk/benefit analysis is required. Developing products to diagnose, mitigate, or treat rare diseases is challenging because of the limited size of the affected population – which makes establishing statistically significant clinical evidence harder. To address this challenge, FDA's Center for Devices and Radiological Health implemented a regulatory pathway uniquely tailored for devices that impact a small number of patients per year. This pathway is defined by two critical steps:

1. HUD Designation – an initial assessment by FDA that focuses on meeting criteria related to the small population of affected individuals, and how that relates to the device being developed.
2. Humanitarian Device Exemption (HDE) Application – a marketing pathway that focuses on proving the device's safety while demonstrating "probable benefit" for the target population.

After completing Steps 1 and 2 with approval, an innovator will be able to legally market their device for the intended (rare) indication.
This article provides clarifying information about how to execute and what to expect when navigating for these steps. The Device Advice page, provided by CDRH Division of Industry and Consumer Education (DICE), is the definitive source for detailed information on this process.

How to Prepare

Know the HUD Designation Process

HUDs are defined as devices intended to treat/diagnose a disease/condition affecting fewer than 8,000 patients in the U.S. per year. The first step in marketing a HUD is obtaining a formal HUD designation from FDA. To receive the designation, the innovator prepares and submits an application that describes the affected population and provides a scientific rationale for development of a unique device for the target population. The application is reviewed by the FDA Office of Orphan Products Development (OOPD, orphan@fda.hhs.gov). OOPD also supports the evaluation of orphan drugs and biologics; a key difference between orphan drugs and HUD is the affected population size, which for orphan drugs is up to 200,000 US patients.

Designation Type	Required U.S. Population Estimate
Humanitarian Use Devices	Incidence ≤ 8,000/year
Orphan Drugs (and Biologics)	Prevalence < 200,000

According to the associated FDA guidance document, the HUD designation application has five key elements:

a) Statement or explanation that disease affects 8,000 individuals per year or less, with exploration of how this estimate may vary in different use cases. The population estimate is very detailed and often complex – it is *not* just a statement of a desired intended use for a rare disease.
b) Contact information for primary contact person.
c) A detailed description of the rare disease or condition and how that relates to the device functionality. This includes a complete device description.
d) The scientific rationale for using the device to treat this rare disease/condition.
e) Authoritative references to support element a) above.

After compiling these elements and submitting them to FDA, FDA will either grant an HUD designation or request additional information. If FDA raises concerns about the humanitarian use which cannot be addressed, particularly around the HUD qualifications, the device may be more suited for an existing device marketing pathway, e.g., 510(k), De Novo, or Premarket Approval (PMA), rather than an HDE.

Know the HDE Process

Although HUD designation opens a pathway to market authorization via an HDE, it also comes with restrictions on the marketing of a device. Specifically, there are restrictions on the amount of profit a manufacturer can make from the sale of the device and the population to which it can be marketed. In comparison to the Premarket Approval pathway, which requires proving safety *and efficacy* of the device, the HDE requires proving **only** safety while demonstrating *probable* benefits (the lack of efficacy requirement is the namesake exemption).

If pre-clinical or clinical testing results are not meeting expected levels of benefit, and only support a probable benefit for a new device targeting a limited population, the HDE pathway may be a good option. Thus, the assessment of benefits is a unique part of an HDE and considers factors such as the type, magnitude, likelihood, duration, and stakeholder perspectives on each potential benefit. The limitation on the number of potentially affected patients is also taken into consideration when assessing the device. CDRH provides a thorough guidance document on the HDE process.

To further outline the similarities and differences between HDE and PMA applications, the guidance document includes the following information:

HDE	PMA
Maintain compliant quality management system	(Same) Maintain compliant quality management system
Must file amendments, supplements, and annual reports as needed	(Same) Must file amendments, supplements, and annual reports as needed

HDE	PMA
May require clinical (Institutional Review Board (IRB)/Investigational Device Exemptions (IDE)), non-clinical, and/or animal data to establish device safety	(Same) May require clinical (IRB/IDE), non-clinical, and/or animal data in order to establish device safety
Exempt from establishing reasonable assurance of efficacy	Must establish reasonable assurance of efficacy
75-day review timeline	180-day review timeline
No fee to file	Must pay user fee
Must maintain an IRB or local committee of record	IRB may be needed for investigational use only
Profit restrictions may apply and must state the amount charged for the device	No restrictions on profit
Must establish that there is no comparable device (except another HUD or investigational device)	Comparable devices frequently exist

Like PMAs, an approved HDE requires regulatory upkeep on an annual basis (via an annual report submitted to FDA) and when significant changes occur (via a supplement submitted to FDA detailing the specific change). To learn more about these processes, it may be helpful to review FDA's information on post-approval PMA requirements. The HDE is most closely comparable to a PMA, the regulatory pathway appropriate for the highest risk devices. Therefore, the HDE pathway may not be as beneficial to innovators when their device may be eligible for a 510(k) application. An HDE may require more effort and definitely comes with more marketing restrictions than a 510(k).
For further details on the required contents of an HDE – see Appendix A of the HDE guidance.

Regulatory Resources

- Guidance documents
  - Humanitarian Use Device (HUD) Designations
  - Humanitarian Device Exemption (HDE) Program
  - Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications
  - Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program
- Public FDA databases
  - HDE product database
    - Tip: Read the "Summary of Safety and Probably Benefit" documents within original HDEs to learn about clinical and non-clinical testing overviews, and relevant standards utilized by other HUDs.
  - Product classification (filter by type: Humanitarian)
- FDA webpages
  - Device Advice – Getting an HUD to Market

    - Office of Orphan Products Development
    - The HUD Program
- NIH network
    - Work with program officers and obtain regulatory feedback within NIH
    - Coordinate a meeting with the NIH Small Business Education and Entrepreneurial Development (SEED) Innovator Support Team
- Submission mechanisms
    - CDRH information page on medical device submissions (eCopy, eSTAR). This is a recently updated process to obtain the most up-to-date information from FDA.

What to Expect

Timeline

The HUD designation review process takes up to 45 calendar days − FDA will respond with a decision: approve, disapprove, or request additional information.
The HDE application review process takes up to 75 review days – FDA will either approve or deny the application. The key difference between "review days" and calendar days is that if FDA requests additional information on an HDE application, the review day "clock" is stopped until FDA receives the additional information.

Pre-Submission Meeting with FDA

As with most regulatory applications for unique devices, it is best practice to hold at least one pre-submission meeting with CDRH before embarking on a HUD-designation and HDE. At this meeting, innovators can describe the device, its intended use, and the patient population with FDA, and obtain FDA feedback on key questions. FDA's feedback can be incorporated into the HUD designation request and/or the HDE application.

Profit Restrictions

Businesses developing and marketing HUDs should be mindful about restrictions placed on profiting from HDE-approved device sales. Essentially there are three scenarios in which the device is eligible to be sold for profit, where the device is intended/labelled to be used to aid in treating or diagnosing:

1. A condition that exists in pediatric (< 22 years old) populations only.
2. A condition that exists in adult (≥ 22 years old) populations only.
3. A condition that exists at all ages, but in pediatric populations at such low frequency that the development of the device would be "impossible or highly impractical."

An example of a product that could not be sold for profit is one that affects all ages and could feasibly be developed with inclusion of pediatrics.
If an innovator seeks to sell a HUD for profit, they need to justify that one of the above criteria applies as part of their HDE application.

General Tips

- An essential part of an HDE is establishing no comparable products exist on the market (via a process such as PMA, 510(k), or De Novo) and obtaining a HUD designation for the device. If the innovator can obtain a 510(k) for their humanitarian device, they should – the 510(k) is generally a less burdensome and less restricted path towards marketing their device.
- Each use of an HDE marketed device must be accompanied by IRB approval of its use in the effected individual. Because of this requirement, many payors consider HDE devices to be experimental and receiving payment for the device can be challenging.
- A device might be applicable to a larger potential population through additional validation. However, the innovator determines if limiting the intended population and indication for use to qualify the device as a HUD outweighs the HDE marketing limitations. The HDE may be an initial pathway to market while additional evidence of benefit is obtained and before the intended population is expanded to the point where a traditional premarket application will be required.
- Though similar, HDEs and IDEs are distinct FDA designations that serve different purposes. An HDE is an open-ended marketing designation, while an IDE is a designation used only during clinical investigations while developing of a device. It is possible that a device would require an IDE (to obtain clinical data on device safety) before applying for an HDE.
- Specifically, a humanitarian use device is designed to ***treat or diagnose*** a disease or condition that affects ≤8,000 individuals in the U.S. per year. This is important because devices used for disease ***prevention*** cannot be HUD designated per FDA regulations.