

# **Humanitarian Device Exemption (HDE) Regulation: Questions and Answers; Final Guidance for Industry**

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**U.S. Department Of Health and Human Services  
Food and Drug Administration  
Center for Devices and Radiological Health**

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# Preface

## Public Comment

Comments and suggestions may be submitted at any time for Agency consideration to Dockets Management Branch, Division of Management Systems and Policy, Office of Human Resources and Management Services, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD, 20852. When submitting comments, please refer to the exact title of this guidance document. Comments may not be acted upon by the Agency until the document is next revised or updated.

For questions regarding the use or interpretation of this guidance contact the HDE Staff at (301) 594-1190.

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# Humanitarian Device Exemption (HDE) Regulation Questions and Answers; Final Guidance for Industry

*This document is intended to provide guidance. It represents the Agency's current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind the Food and Drug Administration (FDA) or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute and regulations.*

## The Least Burdensome Approach

We believe we should consider the least burdensome approach in all areas of medical device regulation. This guidance reflects our careful review of the relevant scientific and legal requirements and what we believe is the least burdensome way for you to comply with those requirements. However, if you believe that an alternative approach would be less burdensome, please contact us so we can consider your point of view. You may send your written comments to the contact person listed in the preface to this guidance or to the CDRH Ombudsman. Comprehensive information on CDRH's Ombudsman, including ways to contact him, can be found on the Internet at <http://www.fda.gov/cdrh/resolvingdisputes/ombudsman.html>.

## Questions and Answers

### 1. What is a Humanitarian Device Exemption (HDE)?

A Humanitarian Device Exemption (HDE) is an application that is similar to a premarket approval (PMA) application, but exempt from the effectiveness requirements of a PMA. An approved HDE authorizes marketing of a Humanitarian Use Device (HUD).

### 2. What is a Humanitarian Use Device (HUD)?

As defined in the Federal Food, Drug, and Cosmetic Act (the act), a HUD is a device that is "intended to benefit patients in the treatment and diagnosis of diseases or conditions that affect fewer than 4,000 individuals in the United States." In the final regulation, however, FDA added the qualifying phrase "per year" to the defining criteria. As the agency explained in the preamble to the final rule, FDA believes that "a point prevalence definition would be considerably more restrictive and provide less of an incentive for the development of such

devices.” FDA also added the phrase “or is manifested” to the definition of a HUD “to establish that [a] HUD designation may be appropriate in cases where more than 4,000 people have the disease but fewer than 4,000 manifest the condition.” (61 FR 33233, June 26, 1996) Therefore, the final definition of a HUD is a device that is intended to benefit patients in the treatment and diagnosis of diseases or conditions that affect or is manifested in fewer than 4,000 individuals in the United States per year.

**3. When does FDA make the determination that the disease or condition affects or is manifested in fewer than 4,000 individuals in the United States per year?**

FDA makes this determination at the time of the request for HUD designation.

**4. Where does an applicant submit a request for a HUD designation?**

Before submitting an HDE application, the applicant should submit a request for a HUD designation to FDA’s Office of Orphan Products Development (OOPD). The request should include: 1) a statement that the applicant is requesting a HUD designation for a rare disease or condition, 2) the name and address of the applicant, 3) a description of the rare disease or condition for which the device is to be used, 4) a description of the device, and 5) documentation, with appended authoritative references, to demonstrate that the device is designed to treat or diagnose a disease or condition that affects or is manifested in fewer than 4,000 people in the U.S. per year (see 21 CFR 814.102(a)). For questions on submitting a HUD designation request or for more information on how the HUD designation determination is made, OOPD may be contacted at (301) 827-3666.

**5. Would an HDE be approved if the applicant establishes that the affected patient population is fewer than 4,000 per year, but each patient may require more than one contact with the device?**

FDA recognizes that, in some cases, the number of patient contacts with a device may exceed one per patient. Such devices may still qualify for HUD designation as long as the total number of patients treated or diagnosed with the device is less than 4,000 per year in the United States.

**6. What is meant by the requirement that no comparable device is available to treat or diagnose the disease or condition?**

One of the criteria that must be satisfied in order for a device to receive marketing approval under this regulation, is that no comparable device, other than another HUD approved under the HDE regulation or a device being studied under an approved IDE, is available to treat or diagnose the disease or condition. Thus, FDA may still approve an HDE even if a comparable device is available under an HDE or an IDE. Once a device with the same intended use as the HUD is approved through the premarket approval (PMA) process or

cleared through the premarket notification (510(k)) process, an HDE cannot be granted for the HUD device.

**7. What is considered a “comparable device”?**

A “comparable device” need not be identical to the device that is the subject of the HDE application. In determining whether a comparable device exists, FDA will consider the device's intended use, technological characteristics, and the patient population to be treated or diagnosed with the device. In addition, FDA will consider if the device meets the needs of the identified patient population, and is therefore, considered a comparable device.

**8. How should an HDE applicant verify that the amount charged does not exceed the costs of research and development, fabrication, and distribution?**

If the amount charged is \$250.00 or more, FDA requires an HDE applicant to obtain a report by an independent certified public accountant, or in lieu of such a report, an attestation by a responsible individual of the organization, verifying that the amount does not exceed the cost of research, development, fabrication, and distribution. If the amount charged is less than \$250.00, FDA will waive this requirement.

**9. How long does FDA have to review an original HDE application?**

The agency has 75 days from the date of receipt to review an HDE application. This includes a 30 day filing period in which the agency determines whether the HDE application is sufficiently complete to permit substantive review. If FDA notifies the HDE applicant that the application is incomplete and cannot be filed, the 75 day timeframe resets upon receipt of the additional information.

**10. Does the Quality Systems Regulation (previously known as the Current Good Manufacturing Practices Regulation) apply to HDEs?**

Yes, but FDA will primarily focus on those manufacturing practices the agency deems most relevant to the safety of the device.

**11. Can an HDE applicant request an exemption from the Quality Systems Regulation?**

Yes. An HDE applicant or holder who believes that he/she cannot comply with or should not be held to GMP standards may request an exemption from the Quality Systems Regulation. In evaluating such a request, FDA will give overriding consideration to the risks posed by the device, the potential risks that a manufacturing defect might pose, and the public health need for the device.

**12. What are the review timeframes for HDE amendments and supplements?**

The review timeframe for HDE amendments and supplements is 75 days, the same as for HDE originals, except for a change submitted in a 30-day supplement (21 CFR 814.39(e)) or a 30-day notice (21 CFR 814.39(f)).

**13. Are amendments and supplements for HDEs subject to the same regulations as those for PMAs?**

HDE amendments and supplements are subject to the same regulations as those for PMAs. In accordance with the HDE regulation, however, an applicant seeking a new indication for use of an approved HUD must obtain a HUD designation for the new indication for use and submit a new original HDE. An application for a new indication may incorporate by reference any information or data previously submitted to FDA in the HDE for the original indication.

**14. Are HDE holders required to submit to FDA the names and addresses of the reviewing Institutional Review Boards (IRBs)?**

No. HDE holders are not required to submit the names and addresses of reviewing IRBs to FDA. As required by section 814.126(b)(2), however, records of the names and addresses of the facilities to which the HUD has been shipped, correspondence with reviewing IRBs, as well as any other information required by a reviewing IRB or FDA must be maintained by the HDE holder.

**15. Who is responsible for ensuring that a HUD is not administered to or implanted in a patient prior to obtaining IRB approval at a health care facility?**

The healthcare provider is responsible for obtaining IRB approval before the HUD is administered to or implanted in a patient. The HDE holder is responsible for ensuring that the HUD is only used in facilities having an IRB constituted and acting in accordance with Part 56.

**16. Why does an IRB need to review and approve the use of the HUD at their institution?**

The statute and the implementing regulation (see 21 CFR 814.124(a)) require IRB review and approval before a HUD is used. (There is an exception to this rule for emergency situations in which the physician determines that approval cannot be obtained in time to prevent serious harm or death to the patient.) As is true for investigational device exemptions (IDEs), the IRB may be a local IRB or it may be an independent or national IRB. In addition, a local IRB may defer in writing to another similarly constituted IRB that has agreed to assume responsibility for review of the use of the HUD.

**17. What types of reviews are IRBs responsible for with respect to HUDs?**

IRBs are responsible for initial as well as continuing review of the HUD. For initial review of a HUD, IRBs are required to perform a full board review. For continuing review, however, IRBs may use the expedited review procedures (section 56.110) unless the IRB determines that full board review should be performed. The agency believes that the expedited review procedures are appropriate for continuing review since the initial review would have been performed by the full board and use of a HUD within its approved labeling does not constitute research.

**18. Does an IRB have to review and approve each individual use of the humanitarian use device (HUD)?**

No. The IRB does not need to review and approve individual uses of a HUD. As long as the use of the HUD is within the FDA approved indication, the IRB may approve use of the device however it sees fit. That is, the IRB may approve use of the HUD without any further restrictions, use of the device under a protocol, or use of the device on a case-by-case basis. In reviewing use of the HUD, IRBs should be cognizant that the use of the device should not exceed the scope of the FDA approved indication.

**19. Is informed consent required when treating/diagnosing a patient with a HUD?**

The Federal Food, Drug, and Cosmetic Act (the act) and the HDE regulation do not require informed consent because an HDE provides for marketing approval, and so use of the HUD does not constitute research or an investigation which would normally require informed consent. Although neither the act nor the regulation requires informed consent, there is nothing in the law or regulation that preempts a state or institution from requiring prospective informed consent. Most HDE holders, however, have developed patient labeling that incorporates information to assist a patient in making an informed decision about the use of the device. That is, the patient labeling contains a discussion of the potential risks and benefits of the device as well as any procedures associated with the use of the HUD. It also states that the device is a humanitarian use device for which effectiveness for the labeled indication has not been demonstrated.

**20. What happens to an approved HDE if, subsequently, FDA makes the determination that the disease or condition affects or is manifested in more than 4,000 individuals in the United States (U.S.) per year?**

If FDA makes the determination that more than 4,000 individuals in the U.S. are affected or manifest a certain disease or condition per year, the agency would need to decide if the HDE should be withdrawn. In making this decision, FDA would consider factors such as the number of patients with the disease/condition, the feasibility of conducting a pivotal clinical trial to demonstrate safety and effectiveness, and the public health need for the device.

**21. If a device gets approved through the PMA process or cleared through the 510(k) process, what happens to the HUD that was approved through an HDE?**

If a device is approved through the PMA process or cleared through the 510(k) process and the labeled indication for the PMA/510(k) is the same as that for the HUD or includes the indication as that for the HUD, FDA may need to rescind the HDE. That is, once a comparable device, the safety and effectiveness of which has been demonstrated, is available to treat or diagnosis the disease or condition, there would no longer be a need for the HUD and the agency may rescind the HDE.

**22. What if the HDE holder decides to collect safety and effectiveness data to support a PMA? Is an IDE needed? Is IRB approval and informed consent required?**

An HDE holder may collect safety and effectiveness data to support a PMA under the approved HDE (i.e., no IDE is needed). If the HUD is the subject of a clinical investigation, (one in which safety and effectiveness data is being collected to support a PMA), IRB approval and informed consent are required. (21 CFR Parts 56 and 50).

**23. In an emergency situation, can a HUD be used off-label (i.e., outside of its approved indications for use)?**

Yes. HUDs may be used off-label in an emergency situation, but certain patient protection measures should be followed before the use occurs. Because IRB review and approval is required before a HUD is used within its approved labeling, a HUD should not be used outside of its approved labeling without similar restrictions. That is, in an emergency situation, a HUD may be used off-label to save the life or protect the physical well-being of a patient, but the physician and HDE holder should follow the emergency use procedures governing such use of unapproved devices.<sup>1</sup> According to this policy, before the device is used, if possible, the physician should obtain the IRB chairperson's concurrence, informed consent from the patient or his/her legal representative, and an independent assessment by an uninvolved physician. In addition, authorization from the HDE holder would be needed before the emergency use of the HUD. After the emergency use occurs, the physician should submit a follow-up report on the patient's condition and information regarding the patient protection measures to the HDE holder, who would then submit this report as an amendment to the HDE.

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<sup>1</sup> See 'Emergency Use of Unapproved Medical Devices' within Chapter III, Expanded Access to Unapproved Devices of the "IDE Policies and Procedures Guidance" at:

[www.fda.gov/cdrh/ode/idepolcy.html](http://www.fda.gov/cdrh/ode/idepolcy.html) For emergency use of a HUD, the HDE holder would assume the responsibilities of the IDE sponsor in this guidance.



**24. What if the situation is not an emergency, but the physician determines that there is no other alternative device for the patient's condition? Can a HUD be used under this type of situation (i.e., compassionate use)?**

Yes, a HUD may be used for compassionate use. As discussed above for emergency use, the physician should ensure that the patient protection measures are addressed before the device is used. In addition to addressing the patient protection measures, prior FDA approval of the HUD for compassionate use is required just as it is for compassionate use of any unapproved device. According to the agency's policy on compassionate use,<sup>2</sup> a physician who wishes to use a device for compassionate use should provide the IDE sponsor with a description of the patient's condition and the circumstances necessitating treatment with the device, a discussion of why alternative therapies are unsatisfactory, and information to address the patient protection measures. For compassionate use of a HUD, the physician should provide this information to the HDE holder, who would then submit it as an HDE amendment for FDA approval before the use occurs. FDA will review the information in an expeditious manner and issue its decision to the HDE holder.

If the request is approved, the physician should devise an appropriate schedule for monitoring the patient, taking into consideration the limited information available regarding the potential risks and benefits of the device and the specific needs of the patient. Further discussion of the post-approval procedures for compassionate use cases, including the submission of a follow-up report to FDA, can be found in the above referenced guidance.

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<sup>2</sup> See 'Individual Patient Access to Investigational Devices Intended for Serious Diseases' within Chapter III of the "IDE Policies and Procedures Guidance" at [www.fda.gov/cdrh/ode/idepolicy.html](http://www.fda.gov/cdrh/ode/idepolicy.html). For compassionate use of a HUD, the HDE holder would assume the responsibilities of the IDE sponsor in this guidance.