FDA has issued a draft guidance, for public comment purposes only, revising some portions of the July 18, 2006 guidance currently in effect. If you wish to review the draft available for comment, please see "Draft Guidance for HDE Holders, Institutional Review Boards (IRBs), Clinical Investigators, and FDA Staff - Humanitarian Device Exemption (HDE) Regulation: Questions and Answers."

Guidance for Industry and FDA Staff

Humanitarian Device Exemption (HDE) Regulation: Questions and Answers

Document issued on: July 18, 2006

This document supersedes Humanitarian Device Exemptions (HDE) Regulation: Questions and Answers, issued July 12, 2001

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U.S. Department of Health and Human Se
Food and Drug Administr
Center for Devices and Radiological H

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Preface

Public Comment

Written comments and suggestions may be submitted at any time for Agency consideration to the Division of Dockets Management, 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.

Additional Copies

Additional copies are available from the Internet at: http://www.fda.gov/cdrh/ode/guidance/1381.pdf. You may also send an e-mail request to dsmica@fda.hhs.gov to receive an electronic copy of the guidance or send a fax request to 240-276-3151 to receive a hard copy. Please use the document number (**1381**) to identify the guidance you are requesting.

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Guidance for Industry and FDA Staff

Humanitarian Device Exemption (HDE) Regulation: Questions and Answers

This guidance represents the Food and Drug Administration's (FDA'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 FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

Introduction

This guidance answers commonly asked questions about Humanitarian Use Devices (HUDs) and applications for Humanitarian Device Exemption (HDE) authorized by section 510(m)(2) of the Federal Food, Drug, and Cosmetic Act (the act). This update of the version issued in 2001 reflects the comments FDA has received. It also clarifies postmarket aspects related to the regulation of HDEs.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

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/ombudsman/.

The questions below are numbered consecutively, 1-30 to be consistent with the 2001 version of this document, but we've added subheadings for ease of use.

Definitions and Other Basics

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 sections 514 and 515 of the act. FDA approval of your HDE authorizes you to market your Humanitarian Use Device (HUD).

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

As defined in 21 CFR 814.3(n), a HUD is a "medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year."[1]

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 its determination when you a request a HUD designation. You should submit your request for a HUD designation before submitting an application for a HDE. You should include FDA's HUD designation letter in your application.

4. Where do I submit a request for a HUD designation?

Submit 2 copies of your request for a HUD designation to:

Office of Orphan Products Development (OOPD), HF-35
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

5. What is required in a request for HUD designation?

In accordance with 21 CFR 814.102(a), your request must include:

- a statement indicating you are requesting a HUD designation
- the name and address of the applicant
- a description of the disease or condition for which the device is intended
- a description of the device
- documentation, with appended authoritative references, to demonstrate that the device meets the definition of 21 CFR 814.3(n).

[1] See 61 FR 33233, June 26, 1996.

FDA's Office of Orphan Products Development is available at (301) 827-3666, if you have questions about the HUD designation.

See 21 CFR 814.104(a) for more information on each of the above items.

6. Can a device qualify for HUD designation if the affected patient population is fewer than 4,000 per year but there are multiple contacts with the device?

FDA recognizes that, in some cases, the number of contacts with the device may exceed one per patient. We believe a device that involves multiple patient contacts may still qualify for HUD designation as long as the total number of patients is less than 4,000 per year in the US.

7. Can I still submit a HDE application if another comparable device is available to treat or diagnose the disease or condition?

FDA will consider a HDE application when no comparable device is available to treat or diagnose the condition, or if a comparable device is available under an approved HDE application, or being studied under an approved Investigational Device Exemption (IDE)) (21 CFR 814.104(b)(2)). FDA cannot grant a HDE for a HUD device, however, once we allow a comparable device with the same intended use to be marketed through the premarket approval (PMA) process or the premarket notification (510(k)) process.

8. What does FDA consider a "comparable device"?

A "comparable device" need not be identical to the device submitted under your HDE application. In determining whether a comparable device exists, FDA will consider:

- the device's intended use and technological characteristics
- the patient population to be treated or diagnosed with the device
- whether the device meets the needs of the identified patient population.

9. How should you verify that the amount charged for the device does not exceed the costs of research and development, fabrication, and distribution?

In accordance with 21 CFR 814.104(b)(5), if you charge more than $250 for the device, FDA requires you obtain a report by an independent certified public accountant (CPA), or an attestation by a responsible individual of your organization, verifying the amount does not exceed the cost of research, development, fabrication, and distribution. If the amount charged is $250 or less, this requirement is waived.

10. Does the Quality Systems Regulation (QSR) (21 CFR Part 820) 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 I request an exemption from the QSR?

Yes. If you believe you cannot comply with or should not be held to the QSR requirements, you may request an exemption. In evaluating your 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.

FDA's Review of HDE Applications

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

Under the Section 520(m)(2), FDA will grant or deny a HDE application within a total of 75 days from the date of receipt. This includes a 30 day filing period during which we determine whether the HDE application is sufficiently complete to permit substantive review. If FDA notifies you that your application is incomplete and requests additional information, the 75 day time frame will reset upon our receipt of the additional information.

13. What are the review time frames for HDE amendments, supplements, and reports?

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

14. Are amendments, supplements, and reports for HDEs subject to the same regulations as those for PMAs?

HDE amendments, supplements, and reports are generally subject to the same regulations as those for PMAs.[2]

15. Are HDEs subject to User Fees under the Medical Device User Fee and Modernization Act of 2002 (MDUFMA)?

No, user fees for HDEs are waived under MDUFMA.

[2] See 21 CFR 814.106 HDE Amendments and resubmitted HDEs, 21 CFR 814.108 Supplemental applications, and 21 CFR 814.126 Postapproval requirements and reports for information about the respective exceptions to 21 CFR 814.37 PMA amendments and resubmitted PMAs, 21 CFR 814.39 PMA supplements, and 21 CFR 814.82 Postapproval requirements.

The Role of Institutional Review Boards (IRBs)

16. Am I required to submit to FDA the names and addresses of the IRBs that approved the use of my HUD?

No. You are not required to submit the names and addresses of the reviewing IRBs to FDA. As required in 21 CFR 814.126(b)(2), however, you must maintain records of:

- the names and addresses of the facilities to which the HUD was shipped
- correspondence with reviewing IRBs
- any other information required by a reviewing IRB or FDA.

17. Who is responsible for ensuring that a HUD is approved for use by the IRB before the device is used at a health care facility?

The healthcare provider should be responsible for obtaining IRB approval before he or she uses a HUD to treat or diagnose patients.

18. Is IRB approval required before the use of a HUD at a facility?

Yes. In accordance with Section 520(m)(4) of the act and section 21 CFR 814.124(a), IRB approval is required before a HUD is used in a facility, except in emergencies where the physician determines that approval cannot be obtained in time to prevent serious harm or death to the patient. As is true for 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.

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

IRBs should be 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 (21 CFR 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.

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

No. The IRB is not required to review and approve individual uses of a HUD, although it may do so. The IRB may use its discretion to determine how to approve use of the HUD. The IRB may approve use of the HUD, for instance, without any further restrictions, under a protocol, or on a case-by-case basis. In reviewing the use of a HUD, IRBs should be

cognizant that the FDA recommends that the use of the device not exceed the scope of the indication approved in the HDE.

21. Is informed consent required when treating or diagnosing a patient with a HUD?

Neither the act nor the regulations require informed consent for use of a HUD. Because a HDE provides for marketing approval, use of the HUD does not constitute research or an investigation, which would normally require informed consent.

Although informed consent is not required, there is nothing in the statute or regulation that preempts a state or institution from requiring prospective informed consent.

Most HDE holders, however, develop patient labeling that incorporates information to assist a patient in making an informed decision about the use of the HUD. That is, the patient labeling generally contains a discussion of the potential risks and benefits of the HUD and any procedures associated with its use. Patient labeling also should state that the device is a humanitarian use device and effectiveness for the labeled indication has not been demonstrated.

After FDA Approves a HDE

22. What are the post-market requirements for adverse event reporting for HDEs?

You are required under 21 CFR Part 803 Medical Device Reporting to submit a report to FDA whenever a device with an approved HDE may have caused or contributed to a death or serious injury, or has malfunctioned and would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

23. What does the HDE holder need to provide to the FDA in its annual report with respect to the HUD designation?

In accordance with 814.126(b)(1), you must provide FDA with updated information on a periodic basis demonstrating that the HUD designation is still valid, based on the most current and authoritative information available. If, as a result of information in your report, FDA believes that the HUD designation may no longer apply, we may contact you for additional information. In addition, you must provide FDA with information on the number of devices shipped or sold since initial marketing approval, the clinical experience with the device and a summary of any changes made to the device. See 21 CFR 814.126(b)(1) for more information on each of the above items.

24. Can I submit a HDE supplement for a new indication for use of my approved HUD?

No. In accordance with 21 CFR 814.106, if you are seeking a new indication for use of an approved HUD, you must first obtain a HUD designation for the new indication for use and then submit a new original HDE application. In your new application, any information or data submitted in your HDE for the original indication may be incorporated by reference.

25. 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 US per year?

If FDA makes the determination that more than 4,000 individuals in the US are affected or manifest a certain disease or condition per year, the agency may consider whether the HDE should be withdrawn. FDA intends to consider factors such as the number of patients with the disease or condition, the feasibility of conducting a pivotal clinical trial (to demonstrate reasonable assurance of safety and effectiveness), and the public health need for the device.

26. After FDA approves a HDE for a HUD, if FDA subsequently approves a PMA or clears a 510(k) for the device or another comparable device with the same indication, what is the status of the HDE approval?

If FDA subsequently approves a PMA or clears a 510(k) for the HUD or another comparable device with the same indication, we may rescind the HDE approval. Once a comparable device becomes legally marketed through PMA approval or 510(k) clearance to treat or diagnosis the disease or condition, there may no longer be a need for the HUD and the HUD can no longer meet the requirements of Section 520(m)(2)(B) of the act.

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

A HDE holder may collect safety and effectiveness data to support a PMA for the HDE-approved indication without an IDE. FDA considers the study exempt from the requirement for an approved IDE as long as the HUD is used in accordance with the approved indication for use and labeling. IRB approval (21 CFR Part 56) and informed consent (21 CFR Part 50) are still needed, however, as required for FDA-regulated clinical studies. Clinical investigation, however, of a HUD beyond its approved indication (e.g., for a broader or different indication) requires an approved IDE. In addition to the requirement of having an FDA-approved IDE, sponsors of these trials must also comply with the regulations governing IRBs (21 CFR Part 56) and informed consent (21 CFR Part 50).

Using HUDs in Emergency and Compassionate Use Situations

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

Yes. In an emergency situation, a HUD may be used off-label, but FDA recommends you follow certain patient protection measures before use. Because IRB review and approval is required before a HUD is used within its approved labeling, FDA believes similar procedures should apply if you use a HUD outside of its approved labeling. 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; however, in this situation, FDA recommends that the physician and HDE holder follow the same emergency use procedures that govern the use of unapproved devices.[3]

29. What are the procedures that govern the emergency use of an unapproved device?

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, an independent assessment by an uninvolved (i.e., not the referring) physician, and institutional clearance. In addition, the physician should obtain authorization from the HDE holder 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 information as a HDE report to the FDA.

If a HUD is used in an emergency situation, the physician should devise a schedule for monitoring the patient, taking into account the specific needs of the patient and the limited information available about the risks and benefits of the device. See **Guidance on IDE Policies and Procedures** for further discussion of the post-treatment procedures for emergency use cases, including the submission of a follow-up report to FDA.

30. Can a HUD be used for compassionate use if the situation is not an emergency, but a physician determines there is no alternative device for the patient's condition?

Yes, a HUD may be used for compassionate use. As in the case of emergency use, FDA recommends that the physician ensure that patient protection measures discussed above are addressed before the device is used. In addition, we recommend you first obtain FDA approval for compassionate use.

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[3] See **Guidance on IDE Policies and Procedures**: Emergency Use of Unapproved Medical Devices, Chapter III Expanded Access to Unapproved Devices, www.fda.gov/cdrh/ode/idepolcy.html. For emergency use of a HUD, we believe the HDE holder assumes the responsibilities of the IDE sponsor described in the guidance.

FDA believes that a physician who wishes to use a HDE-approved device for compassionate use should provide the HDE holder with:

- a description of the patient's condition and
- the circumstances necessitating use of the device,
- a discussion of why alternative therapies or diagnostics are unsatisfactory
- information to address the patient protection measures.

We also recommend the HDE holder submit the above information in a HDE report for FDA approval before the use occurs to help ensure adequate patient protection. FDA will review the information in the most expeditious manner possible and issue a letter to the HDE holder.

If the physician undertakes a compassionate use, he or she should devise a schedule for monitoring the patient, taking into consideration the specific needs of the patient and the limited information available regarding the risks and benefits of the device for this unapproved use. See **Guidance on IDE Policies and Procedures** for further discussion of the post-approval procedures for compassionate use cases, including the submission of a follow-up report to FDA.