

Draft Guidance for HDE Holders, Institutional Review Boards (IRBs), Clinical Investigators, and FDA Staff

Humanitarian Device Exemption (HDE) Regulation: Questions and Answers

DRAFT GUIDANCE

**This guidance document is being distributed for comment purposes only.
Document issued on: August 5, 2008**

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For questions regarding this document, contact Stephen Rhodes in CDRH at (240) 276-4036 or stephen.rhodes@fda.hhs.gov or Leonard Wilson in CBER at (301) 827-0373 or leonard.wilson@fda.hhs.gov

**When final, this document will supersede Humanitarian Device Exemptions (HDE)
Regulation: Questions and Answers, issued July 12, 2001 and July 18, 2006.**



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Center for Biologics Evaluation and Research

Preface

Additional Copies

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Office of Communication, Training and Manufacturers Assistance, HFM-40
Center for Biologics Evaluation and Research
Food and Drug Administration
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Table of Contents

Introduction..... 1
The Least Burdensome Approach..... 1
Definitions..... 2
HUD Designations and HDE Applications..... 2
Contact Information..... 4
FDA’s Review of HDE Applications..... 5
HDEs and Pediatric Patients..... 6
After FDA Approves an HDE.....9
The Role of Institutional Review Boards (IRBs).....12
Using HUDs in Emergency Situations.....19

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Humanitarian Device Exemption (HDE) Regulation: Questions and Answers

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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This draft guidance answers commonly asked questions about Humanitarian Use Devices (HUDs) and applications for Humanitarian Device Exemption (HDE) authorized by section 510(m)(2)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 draft update of the version issued in 2006 reflects the additional requirements set forth in the Pediatric Medical Device Safety and Improvement Act of 2007.

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 use of the word *must* means that something is required. For the purposes of this guidance, “you” refers to the HDE holder, the Institutional Review Board (IRB), or the clinical investigator depending upon how the question is asked and “we” refers to FDA.

The Least Burdensome Approach

We believe we should consider the least burdensome approach in all areas of medical device regulation. This draft guidance reflects our careful review of the relevant scientific and legal

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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 or CBER 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/>. Contact for the CBER Ombudsman can be found on the Internet at <http://www.fda.gov/cber/inside/ombudsman.htm>.

Definitions

1. 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.”

2. 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 is exempt from the effectiveness requirements of sections 514 and 515 of the Food, Drug, and Cosmetic Act (the Act). FDA approval of an HDE authorizes an applicant to market a Humanitarian Use Device (HUD), subject to certain profit and use restrictions set forth in section 520(m) of the Act. Specifically, as described below, HUDs cannot be sold for profit except in narrow circumstances and they can only be used in a facility after an IRB has approved their use in that facility, except in certain emergencies.

3. What is an HDE holder?

An HDE holder is a person who obtains the Humanitarian Device Exemption (HDE) from FDA.

4. What does it mean to “use” a HUD?

The term “use” in this document, when unmodified, refers to the use of a HUD according to its approved labeling and indication. When a HUD is being used in a study or research, the term “investigational use” will be used.

HUD Designations and HDE Applications

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

In accordance with 21 CFR 814.102(a) the applicant’s request must include:

- a statement indicating that the applicant is requesting a HUD designation for a rare

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- disease or condition or a valid subset of the disease or condition
- the name and address of the applicant
- a description of the rare disease or condition for which the device is to be used, the proposed indication or indications for use of the device, and the reasons why such therapy is needed
- a description of the device and a discussion of the scientific rationale for the use of the device for the rare disease or condition
- documentation, with appended authoritative references, to demonstrate that the device meets the definition of 21 CFR 814.3(n).

See 21 CFR 814.102(a) for more information on each of the above items.

6. When does FDA determine whether a device is eligible for designation as a HUD?

We make this determination when an applicant requests a HUD designation. At that time we determine that the device is for a rare disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States (US) per year.

The applicant should submit the request for a HUD designation before submitting an application for an HDE.

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

Yes. FDA recognizes that, in some cases, the number of contacts with the device may exceed one per patient. 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.

8. What is required in an HDE application?

The applicant must include a copy of or reference to FDA's HUD designation letter with the HDE application (21 CFR 814.104(b)(1)). Other contents required in an HDE application are described in detail in 21 CFR 814.104. This information enables FDA to determine whether the device meets the statutory criteria for a HUD set forth in section 520(m)(2) of the Act.

The Pediatric Medical Device Safety and Improvement Act of 2007 (Public Law 110-85) requires additional information in all original HDE applications, if such information is readily available. Specifically, it requires: a description of any pediatric subpopulations that suffer from the disease or condition that the device is intended to treat, diagnose, or

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cure; and the number of affected pediatric patients. See section 515A(a)(2) of the Act.¹

9. Can you submit an HDE application if another comparable device is available to treat or diagnose the disease or condition?

We will consider an HDE application for any of the following:

- no comparable device is available to treat or diagnose the disease or condition; or
- a comparable device is available under another approved HDE application; or
- a comparable device is being studied under an approved Investigational Device Exemption (IDE) (21 CFR 814.104(b)(2)).

However, we cannot grant an HDE for a HUD device once a comparable device with the same indications for use is marketed through either the premarket approval (PMA) process or the premarket notification (510(k)) process. See section 520(m)(2)(B) of the Act.

10. What does FDA consider a “comparable device”?

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

- the device's indications for 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.

Contact Information

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

Submit 2 copies of your request for a HUD designation in accordance with 21 CFR 814.102 to:

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

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

¹ Many of the statutory provisions cited throughout this guidance, including sections 515A(a)(2) and 520(m)(6) of the Act, were added by the Pediatric Medical Device Safety and Improvement Act of 2007.

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12. Where do I submit an HDE application?

Submit 6 copies² of your HDE application in accordance with 21 CFR 814.20 and 814.104 to:

For Products Regulated by CDRH

Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, MD 20850.

For Products Regulated by CBER

Document Control Center (HFM-99)
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Suite 200N
Rockville, MD 20852-1448

FDA's Review of HDE Applications

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

FDA has 75 days from the date of receipt to grant or deny an HDE application. This period includes a 30 day filing period during which we determine whether the HDE application is sufficiently complete to permit substantive review. If we notify the applicant that the application is incomplete and request additional information, the 75 day time frame will reset upon receipt of the additional information by FDA. See section 520(m)(2) of the Act; 21 CFR 814.114.

14. 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 supplement submitted as a 30-day notice (21 CFR 814.39(f)).

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

² We encourage submission of electronic copies. For more information on submission of electronic copies to CDRH, please see "Electronic Copies for Pre-Market Submissions," <http://www.fda.gov/cdrh/electsub.html>. For electronic copies submitted to CBER, please call 301-827-0373.

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Yes. HDE amendments, supplements, and reports are generally subject to the same regulations as those for PMAs. See 21 CFR 814.106, 814.108, 814.110, and 814.126 for specific HDE requirements.

16. Are HDEs subject to user fees?

No. User fees for HDEs are waived under the Medical Device User Fee and Modernization Act of 2002, as reauthorized and amended by the Medical Device User Fee Amendments of 2007.

17. Does the Quality Systems Regulation (QSR) (21 CFR Part 820) apply to HUDs?

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

18. Can I request an exemption from the QSR?

Yes. If you believe that you cannot comply with or should not be held to the QSR requirements, you may request an exemption. As described in 21 CFR 820.1(e), the procedures for petitioning for an exemption are set forth in 21 CFR 10.30. In evaluating such a request, we 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.

HDEs and Pediatric Patients

19. If an HDE was approved for use in pediatric patients prior to the enactment of the Pediatric Medical Device Safety and Improvement Act of 2007, is the HDE holder prohibited from profiting from the sale of the device?

Yes, only original HDE applications for devices indicated for use in pediatric patients or in a pediatric subpopulation that are approved on or after September 27, 2007, are assigned an annual distribution number (ADN) and may be sold for profit (subject to restrictions described below). An HDE supplement by itself is not enough to warrant eligibility for profit if the HDE was previously approved for use in pediatric patients or in a pediatric subpopulation.

20. Are separate HDE applications required for a device indicated for pediatric and adult use?

No. Devices that are intended to treat both a pediatric population and an adult population may be included in a single HDE application, but the indications for use should specify use in pediatric patients or pediatric subpopulation(s) as well as use in adults. In some cases, the safety and probable benefit profile for devices intended for use in a pediatric

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population or in a pediatric subpopulation may differ from its use in an adult population. Therefore, it is recommended that HDE applications for devices intended for use in pediatric populations and adult populations include data supporting the use in both pediatric and adult populations.

We note that the Act, as amended by the Pediatric Medical Device Safety and Improvement Act of 2007 (Public Law 110-85), requires us to establish the annual distribution number (ADN) by assessing projected use of the product in “individuals,” a term that includes both pediatric and adult patients. See section 520(m)(6)(A)(ii) of the Act. This provision authorizes HDE holders to receive profit from the sale of HUDs that are indicated for pediatric use only, or for use in both pediatric and adult patients, subject to the upper limit of the ADN. In this way, when a device is potentially applicable to both pediatric and adult populations, the statute provides an incentive for an applicant to include in its HDE submission to FDA information establishing that the device will not expose pediatric patients to an unreasonable or significant risk of illness or injury and that the probable benefit to health from the use of the device outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment. Only when a submission meets this standard for approval will FDA approve the product for use in pediatric patients, and only then will the HDE holder be eligible to receive profit from the sale of the device.

21. What is the annual distribution number (ADN) and how is it determined?

The Pediatric Medical Device Safety and Improvement Act of 2007 (Public Law 110-85) allows HUDs intended for use in pediatric patients or in a pediatric subpopulation and approved on or after September 27, 2007, to be sold for profit as long as the number of devices distributed in any calendar year does not exceed the annual distribution number (ADN). The ADN is determined by the agency when the agency grants the HDE. It is determined by estimating the number of individuals (pediatric and adult patients) affected by the disease or condition and likely to use the device each year multiplied by the number of devices reasonably necessary to treat each individual. If the number calculated is less than or equal to 4,000, then this number is the ADN. If the number calculated is more than 4,000, then the ADN is 4,000 because in no case can the ADN exceed 4,000 devices. See section 520(m)(6)(A)(ii) of the Act.

In an HDE application, the applicant should provide supporting data for both the number of individuals likely to use the device each year and the number of devices reasonably necessary to treat each such individual. The same principles that govern requests for a HUD designation, specifically documentation with appended authoritative references, should apply to requests for an ADN designation. See question 5 for more information on such documentation.

As stated in section 520(m)(8) of the Act, the agency's Pediatric Advisory Committee will annually review all HUDs intended for use in pediatric patients that are approved on or after September 27, 2007, to ensure that the HDE remains appropriate for the pediatric populations for which it is granted.

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22. After an HDE is approved and an ADN has been assigned, can an HDE holder request to have the ADN modified?

Yes. An HDE holder may submit an HDE supplement (21 CFR 814.108) requesting modification of the ADN based on new information regarding the number of individuals affected by the disease or condition. Again, in no case can the ADN exceed 4,000.

23. Do HDE holders with ADNs set by the agency have special reporting requirements?

HDE holders assigned an ADN must immediately notify the agency if the number of devices distributed in a year exceeds the ADN. See section 520(m)(6)(A)(iii) of the Act. FDA interprets this statutory requirement to mean that HDE holders must immediately notify the agency by submitting an HDE report whenever the number of devices shipped or sold in a year (however they are used) exceeds the ADN.³ In this way, the new statutory notification requirement is generally consistent with the reporting requirement in 21 CFR 814.126(b)(1)(iii) discussed in the “After FDA Approves an HDE” section below (question 32): both concern the number of devices shipped or sold, however the devices are ultimately used (even if outside their approved indications). The only difference is that the new statutory provision requires immediate notification when the number shipped or sold in a year exceeds the ADN, whereas the current regulations require periodic reports on a timeframe specified in the HDE approval order.

24. What happens when the number of devices shipped or sold in a year exceeds the ADN?

For HUDs labeled for use in pediatric patients or in a pediatric subpopulation and approved on or after September 27, 2007, FDA exempts a certain number of these devices each year -- known as the ADN -- from the prohibition on profit (see questions 29 and 30 for more on this prohibition). It is the HDE holder's responsibility to immediately notify the agency in the form of an HDE report (21 CFR 814.126) when the number of the devices shipped or sold in a year (however they are used) exceeds the ADN. Once this notification occurs, or once FDA discovers through an inspection that the ADN has been exceeded, then the general prohibition on profit applies for the remainder of the year. See section 520(m)(6)(D) of the Act.

25. If a device is manufactured in various sizes depending on a patient's anatomy, the number of devices distributed may be more than the number of devices used in any year. Which number, the number used or the number distributed, is the ADN?

As described above, the ADN is the number of devices shipped or sold in a year that the

³ FDA recognizes that HDE holders may ship additional sizes to facilities to ensure that each device fits properly when used. These additional shipments may or may not count towards the annual ADN tally, depending on whether these additional sizes are used or are returned to the HDE holder.

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agency exempts from the prohibition on profit. Once the HDE holder notifies the agency, or once the agency discovers through an inspection, that the AND has been exceeded, sales of the device for the remainder of the year are subject to the general prohibition on profit. If the HDE holder ships multiple sizes, these shipments may or may not count toward the annual ADN tally, depending on whether these additional sizes are used or are returned to the HDE holder (see footnote 3).

26. What is the definition of pediatric patients?

As defined in section 520(m)(6)(E) of the Act, pediatric patients are patients who are 21 years of age or younger at the time of the diagnosis or treatment. A pediatric subpopulation means one of the following populations: neonates, infants, children, or adolescents. FDA reviews pediatric devices through all of its premarket pathways, including premarket notification (510(k)), premarket approval (PMA), biological license application (BLA), and humanitarian device exemption (HDE). Additional information about the definition of pediatric patients and pediatric use can be found in: “Guidance for Industry and FDA Staff: Premarket Assessment of Pediatric Medical Devices,” issued on May 14, 2004, at <http://www.fda.gov/cdrh/mdufma/guidance/1220.html>.

After FDA Approves an HDE

27. Is the HDE holder responsible for ensuring that their HUD is administered only in facilities with IRBs?

Yes. As stated in 21 CFR 814.124(a), the HDE holder is responsible for ensuring that a HUD is administered only in facilities having properly constituted and functioning IRBs. If the local IRB defers the HDE review to another similarly constituted IRB, the local IRB must submit this delegation in a letter to the HDE holder. This submission keeps the HDE holder informed of all reviewing IRBs.

28. Is the HDE holder required to submit to FDA the names and addresses of the IRBs that approved the use of a HUD?

No. The applicant is not required to submit the names and addresses of the reviewing IRBs to FDA. However, as required in 21 CFR 814.126(b)(2), the applicant 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.

29. Does the general prohibition on profit apply to HUDs even when used outside their approved indications?

HUDs, even when used outside their approved indications, are subject to the general

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prohibition on profit. See section 520(m)(3) of the Act; 21 CFR 814.104(b)(5).⁴ As explained in the "HDEs and Pediatric Patients" section above, however, some HUDs are narrowly exempt from this prohibition if they are indicated for use in pediatric patients, or in a pediatric subpopulation, or for use in both pediatric and adult patients, subject to the upper limit of the ADN.

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

If the HDE holder charges more than \$250 for the device, FDA requires a report by an independent certified public accountant (CPA), or an attestation by a responsible individual of the HDE holder's organization, verifying that the amount does not exceed the costs of research, development, fabrication, and distribution (21 CFR 814.104(b)(5)). If the amount charged is \$250 or less, this requirement is waived. Certain HDEs for pediatric use are narrowly exempt from the prohibition against profiting from the sale of the device, as explained in the "HDEs and Pediatric Patients" section above.

31. What adverse event reporting requirements apply to HUDs?

Device user facilities and/or manufacturers are required to submit a report to FDA and to the IRB of record whenever a HUD 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 (21 CFR 814.126(a)). Serious injury means an injury or illness that (1) is life-threatening, (2) results in permanent impairment of a body function or permanent damage to a body structure, or (3) necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure (21 CFR 803.3). The specific requirements for this reporting are set forth in the Medical Device Reporting (MDR) Regulation, at 21 CFR Part 803. Note: pediatric adverse events will be reviewed periodically by the agency's Pediatric Advisory Committee (<http://www.fda.gov/oc/advisory/default.htm>).

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

You must provide us with updated information on a periodic basis demonstrating that the HUD designation is still valid, based on the most current and authoritative information available (21 CFR 814.126(b)). As part of these reporting requirements, you must report the number of devices shipped or sold since initial HDE marketing approval (21 CFR 814.126(b)(1)(iii)). FDA interprets this regulation to require HDE holders to report the total number of devices shipped or sold, no matter how they are used (whether for the

⁴ As discussed in a preamble to the HDE Regulation, "an applicant will not be considered in violation of [section 520(m)(3) of the Act] if [the applicant] receives incidental profits which exceed its good faith estimate of costs." 61 Fed. Reg. 33232, 33242 (June 26, 1996) (citing legislative history).

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approved indication(s), emergency use, or otherwise). The required frequency for these periodic reports is specified in each HDE approval order, as explained in 63 Fed. Reg. 59217, 59218 (Nov. 3, 1998).

If, based on information contained in these reports, we believe that the HUD designation may no longer apply, we may contact you for additional information. See 21 CFR 814.126(b)(1) for more information on these reports.

33. Can an HDE holder submit an HDE supplement for a new indication for use of an approved HUD?

No. 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 the new application, any information or data submitted in the HDE for the original indication may be incorporated by reference. See 21 CFR 814.110.

34. 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 we make the determination that more than 4,000 individuals in the US are affected or manifest a certain disease or condition per year, we may consider whether the HDE should be withdrawn. We intend 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.

35. After FDA approves an 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 we subsequently approve a PMA or clear a 510(k) for the HUD or another comparable device with the same indication, we may withdraw the HDE. Once a comparable device becomes legally marketed through PMA approval or 510(k) clearance to treat or diagnose the disease or condition in question, there may no longer be a need for the HUD and so the HUD may no longer meet the requirements of section 520(m)(2)(B) of the Act.

The Role of Institutional Review Boards (IRBs)

36. What are the differences between an HDE and an IDE? They both use “device exemption” in their titles and can thus be confusing to IRBs.

Quite simply, the term “exemption” for the HDE means certain statutes and regulations need not be followed in order to legally market a HUD. An HDE approval is based on safety and probable benefit; HDEs are exempt from the requirement to provide a

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reasonable assurance of effectiveness, as otherwise required in sections 514 and 515 of the Act.

The term “exemption” for the IDE means certain statutes and regulations need not be followed in order to study an unapproved or uncleared device (or an approved or cleared device for an unapproved or uncleared indication) in a research study involving humans (i.e., an IDE is an investigational exemption). With this exemption, the unapproved or uncleared device can be shipped and used in human research.

37. 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?

You may collect safety and effectiveness data to support a PMA for the HDE-approved indication(s) without an Investigational Device Exemption (IDE). While this is a clinical investigation, FDA considers the study exempt from the requirement for an approved IDE as long as the HUD is used in accordance with its approved indication(s). 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 of a HUD beyond its approved indication(s) (e.g., for a broader or different indication) requires an approved IDE. See 21 CFR 812.20(a)(1). In addition to the requirement of obtaining an FDA-approved IDE, sponsors of these trials must comply with the regulations governing IRBs (21 CFR Part 56) and informed consent (21 CFR Part 50).

38. What are the differences between a PMA, 510(k) and an HDE?

Three regulatory paths to the market for devices are via Premarket Approval (PMA), Premarket Notification (510(k)), and HDE.

A device with an approved PMA is approved for marketing based on valid scientific evidence and reasonable assurance that the device is safe and effective for its intended use. Once approved, it can be marketed and sold within its approved labeling. There are no restrictions on the price, and it can be used by anyone qualified to use the device.

A 510(k) device is cleared for marketing when the agency finds that it is at least as safe and effective, that is, substantially equivalent, to a legally marketed device that is not required to have a PMA. Using valid scientific evidence, submitters compare their device to one or more similar legally marketed devices, comparing the indications for use and technological characteristics.

A device with an approved HDE is approved for marketing, but the approval is based on evidence of safety and probable benefit. The Act and implementing regulations exempt HUDs from the requirement to establish a reasonable assurance of effectiveness. The

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HUD is intended for use in the treatment or diagnosis of a disease or condition that affects or is manifested in fewer than 4,000 individuals in the US per year. The manufacturer of a HUD can make a profit, subject to the limit of the ADN, only if it is indicated for use in a pediatric population or subpopulation or for use in both pediatric and adult patients, was approved on or after September 27, 2007, and with certain other restrictions. (See the “HDEs and Pediatric Patients” section above for further discussion of this narrow profit allowance.) Another important difference is that HUDs require IRB approval before being used at a facility. See sections 520(m)(3), (4), (6) of the Act; 21 CFR 814.124.

39. Should an IRB be concerned if there is a HUD approved for one indication, while the same device is being studied or marketed for another indication that does not qualify for an HDE?

No. A HUD may be used in accordance with its approved indication(s) for use while the same device is being studied under an IDE for a different indication. Additionally, the same device can be approved or cleared for another indication without impacting the HDE.

40. If a HUD is being investigated in an IDE study for a different indication, does it impact the number of allowable patients/users under the HDE?

No. Investigational use of a HUD in an IDE study for a different indication does not impact the HDE approval. The HUD is intended for use in the treatment or diagnosis of a disease or condition that affects or is manifested in fewer than 4,000 individuals in the US per year. The device being investigated in the IDE study for possible subsequent PMA approval or 510(k) clearance will not be for the same indications for use as the HUD.

41. How does an IRB distinguish between the use of a HUD and the study of a HUD in a clinical investigation (i.e., research)?

Prior to manufacturers submitting an HDE application for a device, they must conduct their studies under an IDE (21 CFR Part 812). At this time, most IRBs will not know whether the device is a HUD because the IRB review and approval is for an IDE device being used in a clinical investigation.

Once the HDE is granted, the following information applies if a clinical investigator or the HDE holder wants to conduct a clinical investigation (i.e., research study) using the HUD.

An HDE holder may collect safety and effectiveness data for the HDE-approved indication(s) without an IDE. While this is a clinical investigation, FDA considers the study exempt from the requirement of 21 CFR Part 812 as long as the HUD is being studied in accordance with the approved indication(s) described in labeling, because the HUD as such is legally marketed and can be lawfully shipped without an IDE. See 21

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CFR 812.1. IRB approval (21 CFR Part 56) and informed consent (21 CFR Part 50) are still required for these studies, however, because they are FDA-regulated clinical investigations.

Clinical investigation of a HUD beyond its approved indication(s) (e.g., for a broader or different indication) must be conducted in compliance with 21 CFR Part 812. If the device is Significant Risk (see next question), an FDA-approved IDE is required. See 21 CFR 812.1, 812.20. To date, all HUDs have been significant risk devices. In addition, IRB approval (21 CFR Part 56) and informed consent (21 CFR Part 50) are required.

42. What is the relationship between a HUD and the IRB determination of a Significant Risk (SR) or Non-significant Risk (NSR) device?

When the HUD is used to treat or diagnose patients (i.e., not for research), there is no relationship because an SR/NSR determination applies only to device research studies. Except as provided in question 41, the use of a HUD is not research; it is a legally marketed device, and therefore IRBs need not make the SR or NSR determination. See question 41 for further discussion of the distinction between use of a HUD and investigational use of a HUD in a clinical investigation. For more information about IRB responsibility in making the SR/NSR determination for device research studies, you may refer to the FDA Information Sheets, available at <http://www.fda.gov/oc/ohrt/irbs/default.htm>.

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

Yes. As stated in section 520(m)(4) of the Act, IRB approval is required before a HUD is used at a facility, with the exception of emergency use (see question 65). The IRB must have among its members (or consultants) the appropriate experience and expertise to perform a complete and adequate review of the use of a HUD at that institution (21 CFR 56.107(a)). 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. This deferral letter must be sent to the HDE holder, because the HDE holder is responsible for ensuring that a HUD is administered only in facilities in which the reviewing IRB is constituted and acting in accordance with Part 56 (21 CFR 814.124(a)). See question 46 for further discussion of the scope of IRB approval.

44. Who is responsible for submitting materials to and obtaining approval from the IRB before the HUD is used at a facility?

As explained above, the HDE holder is responsible for ensuring that the HUD is administered only in facilities with properly constituted and functioning IRBs (see question 27). The health care provider at such facilities should be responsible for obtaining IRB approval before use of the HUD, except in certain emergencies where prior IRB approval is not required (see question 65). The IRB should have policies and procedures in place for receipt and evaluation of the materials necessary for initial approval and continuing review of the HUD.

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45. How should an IRB evaluate requests for approval of the use of a HUD?

As stated in 21 CFR 814.124(a), an IRB that reviews and approves the use of a HUD must be constituted and act in accordance with the agency's regulation governing IRBs (21 CFR Part 56), which include continuing review of the use of the device. FDA recommends that an IRB follow the review criteria at 21 CFR 56.111 and elsewhere in Part 56 as much as possible. For example, you should: review the risks to patients that are found in the product labeling and ensure these risks are minimized; and ensure that the risks are reasonable in relation to the proposed use of the device.

Specifically, FDA recommends reviewing the following materials during initial review of the HUD: a copy of the HDE approval order; a description of the device; the product labeling; the patient information packet that may accompany the HUD; a sample consent form for the use of the HUD if required by the IRB; and a summary of how the physician proposes to use the device, including a description of any screening procedures, the HUD procedure, and any patient follow-up visits, tests or procedures. A list of approved HDEs may be found at

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfHDE/HDEInformation.cfm#2>.

The approval order, labeling, and patient information may be found by selecting the number of the appropriate HDE. You should have policies and procedures in place for this review and approval, including whether your IRB requires a consent document for the use of the HUD.

46. To what extent should an IRB exercise oversight of clinician responsibilities in the use of a HUD?

In reviewing the use of the HUD, IRBs should be cognizant that the FDA has made a determination of safety and probable benefit for use of the HUD only within its approved indication(s). The IRB is not required to review and approve each individual use of a HUD. Rather, the IRB may use its discretion to determine how to approve use of a HUD. For example, if it so wishes, with the input of members with the appropriate expertise in the clinical area (21 CFR Part 56), an IRB may specify limitations on the use of the device based upon one or more measures of disease progression, prior use and failure of any alternative treatment modalities, reporting requirements to the IRB or IRB chairperson, appropriate follow-up precautions and evaluations, or any other criteria it determines to be appropriate.

47. 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 their review at a convened meeting (21 CFR 56.108). For continuing review, IRBs may use the expedited review procedures (21 CFR 56.110). When applicable, review of the use of a HUD and review of the investigational use of a HUD in a clinical investigation may be done simultaneously.

Contains Nonbinding Recommendations

Draft – Not for Implementation

48. Why does FDA suggest that an IRB perform the continuing review of a HUD using an expedited procedure?

FDA recommends the use of an expedited procedure because a HUD is a legally marketed device and no safety and effectiveness information is being collected systematically, as is required for a research protocol. An expedited review does not mean a less than substantive review. During the expedited review, the Chair or the Chair's designated member(s) should thoughtfully consider the risk and benefit information available and any Medical Device Reporting (MDR) reports (see question 50). IRBs may develop their own policies and procedures for continuing review of a HUD and may perform this review at a convened meeting.

49. Should other committees at an institution be involved in the review of a HUD?

There is no regulatory requirement for committees other than the IRB to approve the use of a HUD. However, the institution may require additional review. For example, the use of another committee to provide assessments of conflicts of interest, patient risk, or software compatibility may supplement the IRB review.

50. What does an IRB have to know about Medical Device Reporting (MDR)?

The HDE regulations, 21 CFR 814.126(a), require submission of MDR reports to FDA, in accordance with 21 CFR Part 803 (see question 31). Reports submitted to FDA must also be submitted to the IRB of record.

51. What should an IRB consider with respect to the health care provider(s) who will use the HUD?

The IRB may want to ensure that health care providers are qualified through training and expertise to use the device. For many HDEs, the HDE holder is required to provide training on the use of the device prior to the health care provider using the device. Such requirements would be specified in the HDE approval order, available at <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfHDE/HDEInformation.cfm#2> (select the HDE number).

52. Must an IRB request a protocol to review for the use of a HUD?

When a HUD is used to treat or diagnose patients, i.e., not for research, we do not require submission of a protocol to the IRB for review. However, your IRB or institution may require one under its own policies and procedures.

53. Does FDA require an IRB to monitor the number of uses per year of a HUD?

No. It is the responsibility of the HDE holder to monitor how many devices are distributed each year, and if that number exceeds 4,000, to provide an explanation and estimate of how the device is being used by patients. See 21 CFR 814.126(b)(1)(iii).

Contains Nonbinding Recommendations

Draft – Not for Implementation

54. Must an IRB review or audit the medical record of patients who received a HUD?

No, we do not require you to audit medical records of patients who receive a HUD.

55. Should an IRB ask for justification of the charges for the HUD?

No. There is no requirement for the IRB to request a justification of the charges for the HUD. FDA reviews the financial information in the HDE holder's initial application, and periodically thereafter.

56. Should an IRB be concerned if an HDE holder charges for a HUD?

HDE holders generally charge for the HUD that is used to treat or diagnose a patient. However, HUDs cannot be sold for a price that exceeds the costs of research and development, fabrication, and distribution of the device, except if they are indicated for use in a pediatric population, or pediatric subpopulation, or for use in both pediatric and adult patients, were approved on or after September 27, 2007, and annual sales have not yet exceeded the ADN (as discussed in "HDEs and Pediatric Patients" section above). See sections 520(m)(4), (6) of the Act.

If a HUD is studied in a clinical investigation of a new use, the sponsor of the clinical investigation may not charge subjects or investigators a price larger than necessary to recover the costs of manufacture, research, development, and handling (21 CFR 812.7(b)). Any costs for which the subject in a clinical investigation is responsible should be clearly explained in the informed consent document (21 CFR 50.25(b)(3)).

57. Does an IRB function as a Data Monitoring Committee for a HUD?

No. You may, however, ask the HDE holder for copies of the reports submitted periodically to FDA describing clinical experience with the device since the HDE was initially approved. This information includes safety information. In this way, information that could have a bearing on human safety would be considered at the time of continuing review.

58. Do the requirements for review of a HUD change if an IRB has a Federal Wide Assurance (FWA) with the Office of Human Research Protections?

No. The use of a HUD is not research; rather, it is use of a legally marketed device. We describe your responsibilities in the Act at section 520(m) and in the implementing regulations at 21 CFR 814.124. We also offer guidance to you in this document. If, however, a HUD is used in a clinical investigation (see question 41), IRBs should follow their FWA requirements and their written procedures for FDA-regulated research.

59. What information should be given to patients before they receive a HUD, and should patients consent to the HUD use?

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Draft – Not for Implementation

Neither the Act nor the regulations require informed consent from patients for the use of a HUD. An IRB may, however, choose to require informed consent that is consistent with the approved labeling when the IRB approves use of the HUD in a facility.

Most HDE holders develop patient information packets that generally contain a discussion of the potential risks and benefits of the HUD and any procedures associated with its use. If patient information packets are available, the IRB should ensure that physicians distribute them to patients prior to their receiving the HUD. Even when an institution requires patients to sign a written consent document that describes the use of the HUD (and which may provide similar information found in the HDE holder's packet), the patient should always receive the HDE holder's patient information packet. For HUD patient information packets, go to <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfHDE/HDEInformation.cfm#2> and select the HDE number. In addition to the above information, many institutions also require informed consent for the surgery or procedure related to the use of the HUD.

If a HUD is studied in a clinical investigation, the informed consent of the subject must be obtained in accordance with FDA regulations at 21 CFR Part 50 (see question 41).

60. If an IRB requires a written consent document for the use of a HUD, what information should be included?

It would be reasonable for the document to include much of the information found in the HDE holder's patient information packet. If no patient information packet is available, you may consider including the following: an explanation that the HUD is designed to diagnose or treat the disease or condition described in the HDE labeling and that no comparable device is available to treat the disease or condition; a description of any ancillary procedures associated with the use of the HUD; a description of the use of the HUD; all known risks or discomforts; and an explanation of the postulated mechanism of action of the HUD in relation to the disease or condition. Also, the patient should receive information about the HUD status of the device, using a sentence that states, "The effectiveness of this device for this use has not been demonstrated." The IRB may decide to include other information.

If the HUD is studied in a clinical investigation, the elements included in the informed consent document must conform to the requirements found in 21 CFR 50.25.

61. Is it appropriate for the HUD labeling and materials to include the phrase "FDA approved"? What other information must the labeling contain?

HUD labeling and materials must be truthful and not misleading. See section 502(a) of the Act. The labeling may state that the device is approved as a HUD for its intended use but must also include the following statement clarifying that effectiveness has not been demonstrated: "Humanitarian Use Device. Authorized by Federal law for use in the [treatment or diagnosis] of [specify disease or condition]. The effectiveness of this

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device for this use has not been demonstrated.” See 21 CFR 814.104(b)(4)(ii) for more information on HUD labeling requirements.

62. What should IRBs tell physicians who want to study a HUD for a new indication?

Physicians who want to study a HUD for a new indication must submit an IDE application to FDA if the device is a significant risk device (see question 41). Physicians may be either the sponsor or investigator of the study or they may want to involve the HDE holder as the sponsor. The investigational use of a HUD under these circumstances is a clinical investigation and must be conducted in accordance with 21 CFR Parts 812, 50, 54, and 56.

63. Does the use of a HUD constitute treatment or research under the Health Insurance Portability and Accountability Act of 1996 (HIPAA)? Does the IRB need to waive a HIPAA authorization for the use or disclosure of protected health information related to the use of a HUD?

The Privacy Rule promulgated at 45 CFR Parts 160 and 164, Subparts A and E pursuant to HIPAA governs the use and disclosure of certain individually identifiable health information (protected health information). An entity that is covered by HIPAA (a covered entity) may use and disclose protected health information without the patient’s authorization if the use or disclosure is for the purpose of treatment. If the use or disclosure of protected health information is for the purpose of research, then the covered entity generally must obtain the patient’s authorization, unless an IRB or Privacy Board has determined that such an authorization is not necessary because the research satisfies certain waiver criteria.

The use of a HUD according to its approved labeling and indication is generally for treatment or diagnosis, even though such use requires IRB approval. If a HUD is being used according to its approved labeling and indication, and not in a clinical investigation, then protected health information about a patient may be used or disclosed for treatment or diagnostic purposes without the patient’s authorization under HIPAA.

If a HUD is being used in a clinical investigation, whether or not the use of the HUD is the subject of the investigation, then protected health information about a patient that is used or disclosed for purposes of the clinical investigation requires the patient’s authorization under the HIPAA Privacy Rule. The IRB may waive this authorization if certain waiver criteria are met.

64. Does reporting of safety and effectiveness data to the sponsor require a HIPAA authorization or does this activity fall under an FDA-related activity under 45 CFR 164.512(b) (public health reporting)?

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Reporting HUD safety information to the sponsor does not require a HIPAA authorization since it falls under the permissive disclosure for FDA-related activities at 45 CFR 164.512(b)(iii).

Using HUDs in Emergency Use Situations

65. When can a HUD be used without prior IRB approval?

If a physician in an emergency situation determines that IRB approval for the use of the HUD at the facility cannot be obtained in time to prevent serious harm or death to a patient, a HUD may be used without prior IRB approval. The physician must report the emergency use within five days; provide written notification of the use to the IRB chair person including identification of the patient involved, the date of the use, and the reason for the use. See section 520(m)(4) of the Act; 21 CFR 814.124.

66. After an IRB approves the use of the HUD at the facility, can a physician use a HUD outside its approved indication(s) in an emergency or if the physician determines there is no alternative device for the patient's condition?

If a HUD is used outside its approved indication(s), FDA recommends that the physician obtain informed consent from the patient and ensure that reasonable patient protection measures are followed, such as devising schedules to monitor the patient, taking into consideration the patient's specific needs and the limited information available about the risks and benefits of the device. FDA further recommends that the physician submit a follow-up report on the patient's condition to the HDE holder. Note: as discussed in question 31, MDR reports must be submitted to FDA and to the IRB of record if the device may have caused or contributed to death or serious injury and for certain malfunctions.