

# Humanitarian Device Exemption (HDE): Questions and Answers

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## Draft Guidance for HDE Holders, Institutional Review Boards, Clinical Investigators, and Food and Drug Administration Staff

### *DRAFT GUIDANCE*

**This guidance document is being distributed for comment purposes only.**

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You should submit comments and suggestions regarding this draft document within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to <http://www.regulations.gov>. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this document, contact HDE Staff, Center for Devices and Radiological Health (CDRH), at 301-796-5640 or the Office of Communication, Outreach and Development, Center for Biologics Evaluation and Research (CBER), at 1-800-835-4709 or 301-827-1800.

**When final, this document will supersede “Guidance for HDE holders, Institutional Review Boards (IRBs), Clinical Investigators, and Food and Drug Administration Staff, Humanitarian Device Exemptions (HDE) Regulation: Questions and Answers,” issued July 8, 2010.**



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# Preface

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### **CDRH**

Additional copies are available from the Internet. You may also send an e-mail request to [CDRH-Guidance@fda.hhs.gov](mailto:CDRH-Guidance@fda.hhs.gov) to receive a copy of the guidance. Please use the document number (1668) to identify the guidance document you are requesting.

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### **OOPD**

Additional copies of this guidance document are also available from the Office of Orphan Products Development (OOPD), Office of Special Medical Programs, Food and Drug Administration, 10903 New Hampshire Ave, Silver Spring, MD 20993, or by calling 301-796-8660, or from the Internet at <http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/default.htm>. You may also send an e-mail request to [orphan@fda.hhs.gov](mailto:orphan@fda.hhs.gov).

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DRAFT

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## Draft Guidance for HDE Holders, Institutional Review Boards, Clinical Investigators, and Food and Drug Administration Staff

*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 the Humanitarian Device Exemption (HDE) authorized under section 520(m) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act). Section 613 of the Food and Drug Administration Safety and Innovation Act (FDASIA) (Pub. L. 112-144), signed into law on July 9, 2012, amended section 520(m) of the FD&C Act. This guidance document also reflects changes in the HDE program resulting from FDASIA.

HUDs are medical devices intended to benefit patients in the treatment or diagnosis of diseases or conditions that affect or are manifested in fewer than 4,000 individuals in the United States per year.<sup>1</sup> The HDE application is the second step in seeking marketing approval of a HUD. For more information on the first step of the marketing approval process, the preparation and submission of a HUD designation request to the U.S. Food

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<sup>1</sup> 21 CFR 814.3(n).

and Drug Administration (FDA or Agency), Office of Orphan Products Development (OOPD), see the FDA guidance *Humanitarian Use Device (HUD) Designations*, issued on January 24, 2013 (“HUD Designations Guidance”).<sup>2</sup>

For the purposes of this guidance, “you” or “I” 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.

FDA 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.

## **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)?**

As defined in 21 CFR 814.3(m), an HDE is a “premarket approval application” submitted to FDA pursuant to Subpart A, 21 CFR Part 814 “seeking a humanitarian device exemption from the effectiveness requirements of sections 514 and 515 of the [FD&C Act] as authorized by section 520(m)(2) of the [FD&C Act].” HDE approval is based upon, among other criteria, a determination by FDA that the HUD will not expose patients to an unreasonable or significant risk of illness or injury and the probable benefit to health from use of the device outweighs the risk of injury or illness from its use while taking into account the probable risks and benefits of currently available devices or alternative forms of treatment. Section 520(m)(2)(C) of the FD&C Act; 21 CFR 814.104(b)(3). In addition, to be eligible for HDE approval, FDA must determine that the device would not be available to a person with the disease or illness in question without the HDE approval and that there is no comparable device, other than another device approved under an HDE or Investigational Device Exemption (IDE), available to treat or diagnose the disease or condition. Section 520(m)(2)(B) of the FD&C Act; 21 CFR 814.104(b)(2).

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<sup>2</sup> Available at

<http://www.fda.gov/downloads/ForIndustry/DevelopingProductsforRareDiseasesConditions/DesignatingHumanitarianUseDevicesHUDS/LegislationRelatingtoHUDsHDEs/UCM336515.pdf>.

FDA approval of an HDE authorizes an applicant to market a HUD, subject to certain profit and use restrictions. HUDs approved under an HDE cannot be sold for profit, except in certain circumstances, and they can be used in a facility only after an IRB has approved their use in that facility, except in certain emergencies. See question 17 for more on profit and questions 60 and 61 for more on emergency use.

### **3. Who is an HDE holder?**

For purposes of this guidance, an HDE holder is a person who or entity that obtains the approval of an HDE from FDA.

### **4. What does it mean to “use” a HUD?**

The term “*use*” in this document, when unqualified, refers to the use of a HUD approved under an HDE in accordance with its approved labeling and indication(s) to treat or diagnose patients.

## **HUD Designations and HDE Applications**

### **5. How do HDE applicants know if their device is eligible for HDE approval?**

Before submitting an HDE application to FDA, an HDE applicant must first prepare and submit a HUD designation request to OOPD and receive HUD designation. See 21 CFR 814.102(a). In the review of a HUD designation request, FDA will determine whether the device is for a rare disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year. In the case of a device used for diagnostic purposes, FDA will determine whether the documentation demonstrates that fewer than 4,000 individuals per year would be subjected to diagnosis by the device in the United States. See 21 CFR 814.102(a)(5). For more information on the preparation and submission of HUD designation requests, see the HUD Designations Guidance.<sup>3</sup> After receiving HUD designation, the HDE applicant may submit an HDE application to the appropriate assigned center (CDRH or CBER).

Note that if your device is part of a combination product and you are interested in the HDE pathway, an HDE may not suffice as a path to market. For questions about marketing pathways and regulatory requirements for combination products, please contact the Office of Combination Products by phone at 301-796-8930 or by e-mail at [combination@fda.gov](mailto:combination@fda.gov).

### **6. What is required in an HDE application?**

The applicant must include in the HDE application:

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<sup>3</sup> See HUD Designation Guidance, *supra* note 1.

- 1) A copy of or reference to FDA’s HUD designation letter (21 CFR 814.104(b)(1))<sup>4</sup>;
- 2) An explanation of why the HUD would not be available unless an HDE were granted and a statement that no comparable device (other than another HDE-approved HUD or a device under an approved IDE) is available to treat or diagnose the disease or condition. The application also shall contain a discussion of the risks and benefits of currently available devices or alternative forms of treatment in the United States (21 CFR 814.104(b)(2));
- 3) An explanation of why the probable benefit to health from 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. Such explanation shall include a description, explanation, or theory of the underlying disease process or condition, and known or postulated mechanism(s) of action of the device in relation to the disease process or condition (21 CFR 814.104(b)(3));
- 4) The amount to be charged for the device and, if the amount is more than \$250, a report by an independent certified public accountant, made in accordance with the Statement on Standards for Attestation established by the American Institute of Certified Public Accountants. In lieu of such a report, sponsors may also submit an attestation by a responsible individual of the organization, verifying that the amount charged does not exceed the costs of the device’s research, development, fabrication, and distribution. If the amount charged is \$250 or less, the requirement for a report by an independent certified public accountant or an attestation by a responsible individual of the organization is waived. See section 520(m)(6)(D) of the FD&C Act; 21 CFR 814.104(b)(5). Even if an HDE applicant requests that FDA consider whether the HUD meets certain eligibility criteria to qualify for profit making (see the section on “Eligibility for Profit” below for a discussion on how to request to make a profit), the applicant must still include this cost calculation in the HDE application. If the number of HDE-approved HUDs shipped or sold in a year for profit exceeds the annual distribution number (ADN) (described in questions 19 and 23), the sales of the device for the remainder of the year are subject to the general prohibition on profit; and
- 5) Other requirements described in 21 CFR 814.104.

Section 302 of the Food and Drug Administration Amendments Act of 2007 (FDAAA), Pub. L. No. 110-85 (2007), the Pediatric Medical Device Safety and Improvement Act of 2007, added section 515A to the FD&C Act, which requires, among other things, the submission of additional information in all original HDE applications, if such information is readily available.<sup>5</sup> Specifically, section 515A of the FD&C Act requires that each new

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<sup>4</sup> See HUD Designation Guidance, *supra* note 1. As noted in that guidance, we encourage applicants to submit an actual copy of the designation letter with their HDE application.

<sup>5</sup> For further discussion of the information required for pediatric uses of medical devices under section 515A, see *Draft Guidance for Industry and Food and Drug Administration Staff - Providing Information about Pediatric Uses of Medical Devices Under Section 515A of the Federal Food, Drug, and Cosmetic*

HDE application include a description, based on readily available information, of any pediatric subpopulations that suffer from the disease or condition that the device is intended to treat, diagnose, or cure, and the number of affected pediatric patients. See section 515A(a)(2) of the FD&C Act.<sup>6</sup>

Applicants wishing to submit a “modular HDE” for their HDE application may use the procedures outlined in the FDA guidance, *Guidance for Industry and FDA Staff Premarket Approval Application Modular Review* (available at <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM089767.pdf>), issued on November 3, 2003. A “modular HDE” for purposes of this guidance is a compilation of sections or “modules” submitted at different times that together become a complete HDE application. HDE applicants should include a copy of or reference to FDA’s HUD designation letter with any HDE modular submission. The modules should conform to the information required for an HDE application (see 21 CFR 814.104). As discussed in question 15, there are no user fees associated with HDE applications. If an applicant would like to submit a modular HDE, please contact the HDE staff at 301-796-5640.<sup>7</sup>

## **7. What does FDA consider a “comparable device”?**

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

- the device’s indications for use and technological characteristics;
- the patient population to be treated or diagnosed with the device; and
- whether the device meets the needs of the identified patient population.

## **8. Can an applicant submit an HDE application if another comparable device is available to treat or diagnose the disease or condition?**

As noted, eligibility for HDE approval rests in part on a determination by FDA that there is no comparable device available to treat or diagnose the disease or condition, except in certain circumstances. See section 520(m)(2)(B) of the FD&C Act. We will consider an HDE application only in one of the following circumstances:

- no comparable device is available to treat or diagnose the disease or condition; or
- the only comparable devices available are under another approved HDE application and/or being studied under an approved IDE (21 CFR 814.104(b)(2)).

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Act (available at

<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM339465.pdf>), issued on February 19, 2013.

<sup>6</sup> Many of the statutory provisions cited throughout this guidance, including sections 515A(a)(2) and 520(m)(6) of the FD&C Act, were added by section 302 of FDAAA, and amended by FDASIA.

<sup>7</sup> For CBER-regulated products, contact the Regulatory Project Manager in the appropriate Product Office.



FDA may refuse to file an HDE application if FDA determines that a comparable device is available (other than under another approved HDE application or a device under an approved IDE) to treat or diagnose such disease or condition for which the approval of the HUD is being sought. See 21 CFR 814.112(a)(2). Furthermore, we cannot approve an HDE application for a HUD if we determine that such a comparable device is available. See section 520(m)(2)(B) of the FD&C Act.

## **Contact Information**

### **9. Where does an applicant submit an HDE application?**

Submit the required number of copies<sup>8</sup> of the HDE application in accordance with 21 CFR 814.104 to:

For Products Regulated by CDRH

U.S. Food and Drug Administration  
Center for Devices and Radiological Health  
Document Control Center – WO66-G609  
10903 New Hampshire Avenue  
Silver Spring, MD 20993-0002

For Products Regulated by CBER

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

## **FDA's Review of HDE Applications**

### **10. If FDA approves my HDE application, does this constitute “FDA approval” of my HUD?**

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<sup>8</sup> Section 745A(b) of the FD&C Act, added by section 1136 of FDASIA, requires applicants to include an electronic copy of certain submission types, including presubmissions and submissions under section 520(m), after issuance of final guidance implementing that provision. FDA issued the guidance *eCopy Program for Medical Devices Submissions* (available at <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM313794.pdf>), on December 31, 2012. Applicants are therefore required to include an eCopy as one of the required copies of their HDE application.

Yes. A device with an approved HDE is approved for marketing, based on evidence that the device will not expose patients to an unreasonable or significant risk of illness or injury and the probable benefit to health from 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. See section 520(m)(2)(C) of the FD&C Act; 21 CFR 814.104(b)(3). If a HUD meets the HDE standards for approval, it is exempt from the requirement of establishing a reasonable assurance of effectiveness that would otherwise be required under sections 514 and 515 of the FD&C Act. See section 520(m)(2) of the FD&C Act. FDA approval of an HDE authorizes an applicant to market a HUD in accordance with approved labeling and indication(s) for use, subject to certain profit and use restrictions set forth in section 520(m) of the FD&C Act.

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

FDA has 75 days from the date of receipt of an HDE application in the appropriate Document Control Center that is accepted for filing to send the HDE applicant an approval order, an approvable letter, a not approvable letter, or an order denying approval. See section 520(m)(2) of the FD&C Act; 21 CFR 814.114. The filing of an HDE means that FDA has made a threshold determination that the application is sufficiently complete to permit substantive review. See 21 CFR 814.112. Within 30 days from the date an HDE is received by FDA, the FDA will notify the HDE applicant whether the application has been filed. See 21 CFR 814.112.

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

The review timeframe for HDE amendments (see 21 CFR 814.106) and supplements (see 21 CFR 814.108) is 75 days, the same as for HDE original applications, except for a supplement submitted as a 30-day notice (21 CFR 814.108, 814.39(f)).

**13. Are HDE amendments, supplements, and reports subject to the same regulations as those for Premarket Approval Applications (PMA)?**

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. See question 33 for more on HDE supplements.

**14. What are some of the differences between HDE and a PMA approval?**

A HUD with an approved HDE is approved for marketing, based upon, among other criteria, a determination by FDA that the HUD will not expose patients to an unreasonable or significant risk of illness or injury and the probable benefit to health from use of the device outweighs the risk of injury or illness from its use while taking

into account the probable risks and benefits of currently available devices or alternative forms of treatment. See section 520(m)(2)(C) of the FD&C Act; 21 CFR 814.104(b)(3).

Devices approved for an HDE are exempt from the requirement of establishing a reasonable assurance of effectiveness. 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. An HDE holder can make a profit on its HUD, subject to the limit of the ADN, only if the device meets the eligibility criteria for the exemption to the profit prohibition in section 520(m)(6)(A)(i), subject to restrictions in section 520(m)(6) of the FD&C Act. (See the “Eligibility for Profit” section below for further discussion of this profit allowance.) HUDs also require IRB approval generally before being used in a facility. See section 520(m)(4) of the FD&C Act; 21 CFR 814.124.

The premarket approval process is the FDA process of scientific and regulatory review to evaluate the safety and effectiveness of class III medical devices. Class III devices are devices that are (1) for a use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health, or presents a potential, unreasonable risk of illness or injury and (2) for which insufficient information exists to determine that general and special controls are sufficient to provide a reasonable assurance of safety and effectiveness. See section 513(a)(1)(C) of the FD&C Act. Generally, PMA approval must be obtained for class III devices under section 515 of the FD&C Act prior to marketing.<sup>9</sup> Once approved, these devices can be marketed and sold within their approved labeling and without restrictions on price.

#### **15. Are HDE applications subject to user fees?**

No. User fees for HDE applications 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 2012.

#### **16. Does the Quality System (QS) Regulation (21 CFR Part 820) apply to HUDs?**

Yes. Compliance with the QS regulation at 21 CFR Part 820 is required. Additional information on manufacturing information to include in an HDE submission can be found in the FDA guidance *Quality System Information for Certain Premarket Application Reviews* (available at <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070899.pdf>), issued on February 3, 2003. If you believe that you cannot comply with or should not be subject to the QS regulation requirements, you may request

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<sup>9</sup> Certain types of devices classified into class III that were in commercial distribution in the United States before May 28, 1976, and those determined to be substantially equivalent to such devices, may be cleared through the 510(k) premarket notification process until FDA publishes orders requiring them to go through the PMA process or reclassifies them into a lower class. Section 515(b)(1) of the FD&C Act.

an exemption or a variance from any device QS regulation requirement. As described in 21 CFR 820.1(e), petitions for an exemption or variance must be submitted according to the procedures set forth in 21 CFR 10.30.

## **Eligibility for Profit**

### **17. What types of HUDs are eligible to make a profit?**

Except in certain circumstances, HUDs approved under an HDE cannot be sold for an amount that exceeds the costs of research and development, fabrication, and distribution of the device (i.e., for profit). Under section 520(m)(6)(A)(i) of the FD&C Act, as amended by FDASIA, a HUD is only eligible to be sold for profit after receiving HDE approval if the device meets the following criteria (for purposes of this guidance, “eligibility criteria”):

1. The device is intended for the treatment or diagnosis of a disease or condition that occurs in pediatric patients or in a pediatric subpopulation, and such device is labeled for use in pediatric patients or in a pediatric subpopulation in which the disease or condition occurs; or
2. The device is intended for the treatment or diagnosis of a disease or condition that does not occur in pediatric patients or that occurs in pediatric patients in such numbers that the development of the device for such patients is impossible, highly impracticable, or unsafe.<sup>10</sup>

If an HDE-approved device does not meet either of the eligibility criteria, the device cannot be sold for profit.

HDE applicants whose devices meet one of the eligibility criteria and wish to sell their HUD for profit should provide adequate supporting documentation to FDA in an original HDE application to demonstrate to FDA that the HUD meets the eligibility criteria. HDE holders whose HDE was approved prior to the enactment of FDASIA who wishes to sell their HUD for profit should provide adequate supporting documentation to FDA in an HDE supplement to demonstrate to FDA that the HUD meets the eligibility criteria. See question 20 for more information about how an HDE holder whose HDE was approved prior to the enactment of FDASIA can request to make a profit. In addition, see the section on “HDEs and Pediatric Patients” below for further discussion on pediatrics.

### **18. What does it mean that a device is intended for the treatment or diagnosis of a disease or condition that “does not occur in pediatric patients” or that “occurs in pediatric patients in such numbers that the development of the device for such patients is impossible, highly impracticable, or unsafe”?**

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<sup>10</sup> See question 18 below for further explanation.

Under section 520(m)(6)(A)(i)(II) of the FD&C Act, a HUD is eligible to be sold for profit after receiving HDE approval if the device is intended for the treatment or diagnosis of a disease or condition that:

- “does not occur in pediatric patients,”

or

- “occurs in pediatric patients in such numbers that the development of the device for such patients is impossible, highly impracticable, or unsafe.”

**Does not occur in pediatric patients** – An example of a disease that does not occur in pediatric patients is Alzheimer’s disease.

**Impossible or highly impracticable** – When determining whether the development of a HUD in pediatric patients is “impossible” or “highly impracticable,” FDA considers information provided by the applicant to FDA, including publicly available information such as published literature, which demonstrates that the sponsor would not be able to conduct the necessary clinical investigation(s) in the pediatric population for the device. For example, FDA may determine that the development of a particular device is “impossible” or “highly impracticable” in pediatric patients if it is intended to treat a disease or condition that has a pediatric annual incidence that is so small or if the pediatric population is so geographically dispersed to prevent sufficient patient recruitment in the pediatric population for a clinical investigation. Because of the speed and efficiency of modern communications tools, geographic dispersion will justify a waiver only in extraordinary circumstances and will generally have to be coupled with very small population size.<sup>11</sup> FDA does not consider economic factors (such as the costs associated with conducting a clinical investigation) as a basis for being “impossible” or “highly impracticable.”

**Unsafe** – FDA may determine that the development of a HUD in pediatric patients is “unsafe” if the applicant has provided information, including publicly available information such as published literature, to FDA that demonstrates that the device would expose pediatric patients to an unreasonable or significant risk of illness or injury. If FDA determines that the HUD is eligible to be sold for profit because development of the device in pediatric patients would be “unsafe,” the labeling (e.g., warnings or contraindications) for the device should reflect the safety concern.

## **19. What is the annual distribution number (ADN) and how is it determined?**

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<sup>11</sup> For a discussion of how the terms “impossible” and “highly impracticable” have been interpreted in the drug context, see 63 Fed. Reg. 66632, 66647 (Dec. 2, 1998) (discussing the high bar of finding that clinical trials are “impossible” or “highly impracticable” in the drugs context).

Under section 520(m)(6) of the FD&C Act, if FDA makes a determination that a HUD meets the eligibility criteria, the HUD is permitted to be sold for profit after receiving HDE approval as long as the number of devices distributed in any calendar year does not exceed the ADN for the device.

The ADN is determined by FDA:

- when the Agency approves the original HDE application; or
- when the Agency approves an HDE supplement for an HDE approved before the enactment of FDASIA on July 9, 2012, if the HDE holder seeks a “determination” for the HUD in an HDE supplement based upon the profit-making eligibility criteria, and FDA determines that the HUD meets the eligibility criteria.<sup>12</sup> See section 520(m)(6)(A)(ii) of the FD&C Act and section 613(b) of FDASIA.

Under section 520(m)(6)(A)(ii) of the FD&C Act, the ADN is defined as the number of devices “reasonably needed to treat, diagnose, or cure a population of 4,000 individuals in the United States.” When determining the ADN, FDA considers the number of devices per year reasonably needed to treat, diagnose, or cure an individual (“first multiplier”) and multiplies that value by 4,000 (“second multiplier”). By law, the second multiplier is always 4,000, regardless of whether the target population estimate is fewer than 4,000 individuals. Therefore, the ADN will be equal to or greater than 4,000, depending on the value of the first multiplier. For example, the target population estimate for the intended use may be 3,000 individuals, but if 2 devices are reasonably needed per year to treat, diagnose or cure a patient, the ADN would be 8,000 (i.e., 2 multiplied by 4,000 because the second multiplier for the ADN is always 4,000, regardless of the actual population estimate).

The applicant should provide the number of devices per year reasonably necessary to treat each individual in the HDE application, and provide adequate supporting documentation to support such number, in order to provide a basis for FDA to calculate the ADN.

**20. If an HDE was approved for use prior to the enactment of FDASIA, is the HDE holder prohibited from profiting from the sale of the device?**

Not necessarily. An HDE holder of a HUD for which an HDE was approved prior to the enactment of FDASIA on July 9, 2012 may submit an HDE supplement (21 CFR 814.108) requesting an exemption from the profit prohibition for a HUD. If FDA determines that the HUD meets the eligibility criteria, FDA will then determine the ADN for the HUD when FDA approves the HDE supplement. See section 613(b) of FDASIA,

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<sup>12</sup> As further discussed in questions 20 and 33, an HDE holder of a HUD for which an HDE was approved prior to the enactment of FDASIA on July 9, 2012 may submit an HDE supplement to FDA for an exemption from the profit prohibition for a HUD.

and question 19 for more discussion on the ADN. The applicant should provide the number of devices per year reasonably necessary to treat each individual in the HDE supplement, and provide adequate supporting documentation to support such number, in order to provide a basis for FDA to calculate the ADN.

**21. 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 that FDA modify the ADN based upon additional information. See section 520(m)(6)(C) of the FD&C Act.

**22. 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 FD&C 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 HUDs shipped or sold in a year, however the HUD is used, exceeds the ADN.<sup>13</sup> The statutory notification requirement is generally consistent with the reporting requirement in 21 CFR 814.126(b)(1)(iii) and discussed in question 32: both requirements concern the number of devices shipped or sold regardless of their ultimate use (even if outside their approved indications). The only difference is that the statutory provision requires immediate notification when the number shipped or sold in a year exceeds the ADN, whereas the current regulations (discussed in question 32) require periodic reports on a timeframe specified in the HDE approval order.

In those rare cases in which a device holds both an HDE approval for a certain indication and a PMA approval for a different indication, sales or shipments of the device pursuant to the PMA approval are not subject to the ADN reporting requirement. The ADN relates only to those devices that are on the market through the HDE review process. Therefore, the manufacturer is required to notify FDA only when sales or shipments tracked pursuant to the HDE exceed the ADN.

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

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 HUDs shipped or sold in a year, regardless of the use of the HUD (unless such use is cleared or approved by FDA under a

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<sup>13</sup> See question 24 for a discussion on whether shipment of multiple sizes to facilities counts towards the ADN.

IDE, 510(k) or PMA), exceeds the ADN. Once this notification occurs, or once FDA discovers through an inspection that the ADN has been exceeded, then the sales of the HUD for the remainder of the year are subject to the general prohibition on profit (unless FDA approves an ADN modification request in an HDE supplement) and the amount charged for the device must not exceed the cost of research and development, fabrication, and distribution of the device. See section 520(m)(6)(D) of the FD&C Act; 21 CFR 814.104(b)(5).

**24. If a device is manufactured in various sizes (to account for differences in patients' 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 used to determine whether the ADN has been exceeded?**

As described above, the ADN is the number of devices distributed (i.e., shipped or sold) in a year that the Agency exempts from the prohibition on profit. FDA recognizes that HDE holders may ship multiple sizes of a device to facilities to ensure that one of the devices properly fits the patient(s) when used. If the HDE holder ships multiple sizes of a device, all of the devices may not count toward the ADN tally if the additional sizes of the devices (that did not properly fit the patient(s)) are returned to the HDE holder. The HDE holder should document in its periodic report how many devices are returned to the HDE holder if multiple sizes are shipped. See question 32 for more information on periodic reports.

## **HDEs and Pediatric Patients**

**25. What is the definition of pediatric patients?**

As defined in section 520(m)(6)(E) of the FD&C Act, pediatric patients for purposes of section 520(m) of the FD&C Act are patients who are 21 years of age or younger (i.e., up to, but not including, the 22<sup>nd</sup> birthday) at the time of the diagnosis or treatment. A pediatric subpopulation means one of the following populations: neonates, infants, children, or adolescents. Additional information about the definition of pediatric patients and pediatric use as it relates to medical devices can be found in the FDA guidance *Premarket Assessment of Pediatric Medical Devices* (available at <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM089742.pdf>), issued on May 14, 2004.

**26. Are separate HDE applications required for a device indicated for both 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



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.

**27. Can devices labeled for pediatric use receive profit?**

Yes. As discussed in question 17, under section 520(m)(6)(A)(i)(I) of the FD&C Act, a HUD is eligible to be sold for profit if the device is “intended for the treatment or diagnosis of a disease or condition that occurs in pediatric patients or in a pediatric subpopulation, and such device is labeled for use in pediatric patients or in a pediatric subpopulation in which the disease or condition occurs.” This provision authorizes HDE holders to receive profit from the sale of HUDs that are indicated and labeled for pediatric use, subject to the limit of the ADN. This may include HUDs approved under an HDE that are indicated and labeled for pediatric use only or for use in both pediatric and adult patients. When a device is 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. Such analysis should address the risks compared to the benefits, 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, at which time the HDE holder is eligible to receive profit from the sale of the device, subject to the ADN.

**28. What is the Pediatric Advisory Committee?**

FDA’s Pediatric Advisory Committee (PAC)<sup>14</sup> annually reviews all HDE-approved devices described in section 520(m)(6)(A)(i)(I) of the FD&C Act. These are HUDs approved under an HDE that are intended and labeled for the treatment or diagnosis of a disease or condition that occurs in pediatric patients or in a pediatric subpopulation in accordance with section 520(m)(6) of the FD&C Act. See section 520(m)(8) of the FD&C Act. The PAC reviews these devices to ensure that the HDE remains appropriate for the pediatric populations for which it is approved, in accordance with section 520(m)(2) of the FD&C Act. The PAC also conducts periodic review of adverse events for these devices.

## **After FDA Approves an HDE**

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<sup>14</sup> For more information on the Pediatric Advisory Committee, see <http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/default.htm>.

**29. Is IRB approval required before a HUD can be used at a facility?**

Yes. A HUD with an approved HDE is approved by FDA for marketing. However, IRB approval is required before a HUD can be used at a facility, with the exception of emergency use (see the section on “Using HUDs in Emergency Use Situations” below for further discussion on emergency use). The HDE holder is responsible for ensuring that a HUD approved under an HDE is administered only in facilities having an IRB constituted and acting in accordance with the Agency’s regulation governing IRBs (21 CFR Part 56), including continuing review of use of the device. See section 520(m)(4) of the FD&C Act; 21 CFR 814.124. The IRB must have members or consultants with 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 oversee 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 21 CFR Part 56 (21 CFR 814.124(a)).

**30. 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 HDE holder 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 HDE holder must maintain records of:

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

These records must be maintained in accordance with the HDE approval order. See 21 CFR 814.126(b)(2).

**31. What adverse event reporting requirements apply to HUDs?**

Device manufacturers and user facilities are required to submit medical device reports to FDA and to the “IRB of record” (i.e., the IRB approving the use of the HUD). (See section 519(a) and (b) of the FD&C Act; 21 CFR 803.30, 803.50, and 814.126(a).) Among these requirements, manufacturers must submit reports to FDA and 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 803.50 and 814.126(a)). User facilities must submit reports to FDA, the IRB of record, and the manufacturer whenever a HUD may have caused or contributed to a death, and must submit reports to the manufacturer (or to FDA and the IRB of record if the manufacturer is unknown) whenever a HUD may have caused or contributed to a serious injury (21 CFR 803.30 and 814.126(a)). Serious injury means an injury or illness that (1) is life-threatening, (2) results in permanent impairment of a bodily function or permanent damage to a body structure, or (3) necessitates medical

or surgical intervention to preclude permanent impairment of a bodily 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. Pediatric adverse events will be reviewed periodically by FDA's PAC. See question 28 for more discussion on the PAC.

**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 to demonstrate that the HUD designation is still valid, based on the most current and authoritative information available (21 CFR 814.126(b)). To demonstrate that the HUD designation is still valid, you must include in a periodic report an updated annual incidence reassessment (AIR) with updated numbers to show that the target population for the disease or condition for which the device has been designated is still under 4,000 per year. Note that the AIR refers to the HUD designated population, which in some cases may be larger than the HDE-approved indication (i.e., if the HDE approval covers only a certain indication within the designated disease or condition). In reviewing this information, the reviewing center, CDRH or CBER, may refer the AIR to OOPD for further evaluation if necessary.

As part of these reporting requirements, you must also 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 HUDs shipped or sold, no matter how the HUDs are used (whether for the approved indication(s), emergency use, or otherwise). However, for devices that have both an HDE approval and a PMA approval for a different indication, you are required to report only on the number of devices that are shipped or sold pursuant to the HDE, unless specifically required by the PMA Approval Order. 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 to your device, we may contact you for additional information or revoke your HUD designation. See 21 CFR 814.126(b)(1) for more information on these reports, and 21 CFR 814.102(c) and question 34 for more information on revocation of HUD designation.

**33. When should an HDE holder submit an HDE supplement versus a new original HDE application?**

If you are seeking a new indication for use of an approved HUD (e.g., for a different disease or condition), you must submit a new original HDE application. 21 CFR 814.110. If you are submitting a new original HDE application, please contact OOPD to discuss obtaining a new HUD designation. In the new HDE application, any relevant

information or data submitted in the HDE for the original indication may be incorporated by reference.

Other changes to an approved HDE (e.g., certain design changes) can be submitted in an HDE supplement. 21 CFR 814.108.

**34. What happens to an approved HDE if, FDA subsequently makes the determination that the disease or condition affects or is manifested in 4,000 or more individuals in the US per year?**

If we make the determination that 4,000 or more individuals in the US are affected or manifest a certain disease or condition per year, we may consider whether your HUD designation should be revoked in accordance with 21 CFR 814.102(c) and your HDE withdrawn in accordance with 21 CFR 814.118. In making this determination, we intend to consider factors such as the number of patients with the disease or condition, the feasibility of conducting a pivotal clinical investigation (to demonstrate reasonable assurance of safety and effectiveness), and the public health need for the device. We may discuss the regulatory options with the HDE holder if this occurs.

**35. If a HUD is being investigated in an IDE study for an indication not approved in the HDE, do HDE applicants need to report the number of devices in the study in their HDE periodic reports?**

No. Investigational use of a HUD in an IDE study for an indication not approved in the HDE does not need to be reported in the HDE periodic report (see question 32 for more information on periodic reports).

**36. What is the status of the HDE approval if, after FDA approves an HDE for a HUD, FDA subsequently approves a PMA or clears a 510(k) for the device or another comparable device with the same indication?**

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 because the HUD would no longer meet the requirements of section 520(m)(2)(B) of the FD&C Act. 21 CFR 814.118(a).

## **The Role of Institutional Review Boards (IRBs)**

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

FDA approval of an HDE authorizes an applicant to market a HUD in accordance with approved labeling and indication(s) for use, subject to certain profit and use restrictions set forth in section 520(m) of the FD&C Act. If a HUD meets the HDE standards for

approval, it is exempt from the requirement of establishing a reasonable assurance of effectiveness that would otherwise be required under sections 514 and 515 of the FD&C Act. See section 520(m)(2) of the FD&C Act.

A device being used under an approved IDE is a device that has not been cleared or approved by FDA for marketing but has been authorized for investigational use in an FDA-regulated clinical investigation (i.e., an IDE is an investigational exemption). With this exemption, the investigational device can be shipped lawfully for the purposes of conducting clinical investigations of the device without complying with certain other requirements of the FD&C Act that would apply to devices in commercial distribution. See 21 CFR Part 812.

**38. Should an IRB be concerned if there is a HUD that is approved under an HDE for one indication, while being studied or marketed for another indication that was not approved under an HDE?**

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

**39. When clinical data are collected for a HUD, what requirements apply?**

Prior to the approval of an HDE application for a device, any clinical investigations using the device must be in compliance with the IDE regulations (21 CFR Part 812). Once the HDE is approved, the following information applies if a clinical investigator or the HDE holder wants to conduct a clinical investigation using the HUD.

Data can be collected in a clinical investigation **for the HDE-approved indication(s)** without an IDE. As long as the HUD is being studied for the indication(s) in its approved labeling, the HUD is not subject to IDE requirements because the HUD is a legally marketed device and therefore can be lawfully shipped without an IDE. See 21 CFR 812.1. However, other clinical investigation requirements still apply, including IRB approval (21 CFR Part 56) and protection of human subjects, including informed consent and, if applicable, additional safeguards for children (21 CFR Part 50).

Clinical investigation of a HUD for a different indication than the HDE-approved indication must be conducted in compliance with the IDE regulations at 21 CFR Part 812, subject to IRB approval (21 CFR Part 56), and in compliance with protection of human subjects, including informed consent and, if applicable, additional safeguards for children (21 CFR Part 50). If the device is a significant risk device, an FDA-approved IDE is required before starting the clinical investigation. See 21 CFR 812.1, 812.20. To date, all HUDs have been significant risk devices requiring FDA-approved IDEs. See question 40 for more discussion of significant risk devices.

Note that IRB approval for the “use” of a HUD at a facility to treat or diagnose patients (see questions 29 and 42) does not mean that the IRB has approved the investigational use of the HUD (i.e., in a clinical investigation). Rather, it has approved only the use of the device for the HDE-approved indication. For more information on the difference between “use” of a HUD and “investigational use” of a HUD, see “Figure 1: Decision Tree for IRB Review of HUDs” at the end of this guidance.

**40. Does an IRB have to make the determination of a significant risk (SR) or non-significant risk (NSR) device (21 CFR 812.66) when it reviews a HUD?**

When an IRB is deciding whether to approve the use of a HUD at a facility (see question 42), its review does not include an SR/NSR determination. As noted above, use of a legally marketed HUD within its HDE-approved indication at a facility to treat or diagnose patients is not a clinical investigation.

In addition, an IRB does not have to make a SR/NSR determination when it receives a request to review a clinical investigation of a HUD (e.g., collection of safety and effectiveness data) when that clinical investigation concerns the HDE-approved indication(s) only. FDA considers such investigations exempt from the IDE requirements in 21 CFR Part 812. Nonetheless, the IRB still has to approve the clinical investigation under 21 CFR Part 56. Note that informed consent and additional safeguards for children (if applicable) are required under 21 CFR Part 50, as for all FDA-regulated clinical studies.

In contrast, if the IRB receives a request to review an application for an investigational study of the HUD for a different indication than the HDE-approved indication, then the IRB should be aware that this type of clinical investigation is subject to the IDE regulations at 21 CFR Part 812. To date, all HUDs studied for uses other than their approved indication(s) have been SR devices requiring an FDA-approved IDE. See 21 CFR 812.20(a). In practice, most sponsors have obtained an IDE from FDA before beginning such studies, so IRBs have not needed to make the SR/NSR determination (i.e., the sponsor already knew the device was a SR device). However, in the event that a sponsor seeks IRB approval for research of a HUD for an indication other than its approved indication(s) without first obtaining an FDA-approved IDE, then the IRB should make the SR/NSR determination as required in 21 CFR 812.66.

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

The HDE holder is responsible for ensuring that the HUD is administered only in facilities with properly constituted and functioning IRBs (see question 29). 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 the section on “Using HUDs in Emergency Use Situations” below for further discussion on emergency use). 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.

**42. 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 addresses requirements relating to initial and continuing review of the use of the device. FDA recommends that an IRB follow the review criteria in 21 CFR 56.111 and elsewhere in Part 56. For example, you should review the risks to patients that are found in the product labeling, ensure the risks are minimized, and evaluate whether the risks are reasonable in relation to the proposed use of the device for their facility.

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.fda.gov/medicaldevices/productsandmedicalprocedures/deviceapprovalsandclearances/hdeapprovals/ucm161827.htm>. The approval order, labeling, and patient information may be found by selecting the submission 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.

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

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. 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).

**44. What types of review functions 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.

**45. 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 under 21 CFR 56.110 because a HDE-approved HUD is a legally marketed device and no safety and effectiveness information is being collected systematically, as would be 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 MDR reports (see question 31). IRBs may develop their own policies and procedures for continuing review of a HUD and may perform this review at a convened meeting.

**46. 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 specific risks posed by the technology or software compatibility may supplement the IRB review.

**47. Must medical device reports be submitted to an IRB?**

The HDE regulation, 21 CFR 814.126(a), requires that MDR reports submitted to FDA, in accordance with 21 CFR Part 803 (see question 31), also be submitted to the "IRB of record" (i.e., the IRB approving the use of the HUD).

**48. 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 HDE-approved HUDs, 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.fda.gov/medicaldevices/productsandmedicalprocedures/deviceapprovalsandclearances/hdeapprovals/ucm161827.htm> (select the HDE number).

**49. Must an IRB request a protocol to review before approving the use of the HUD?**

When a HUD is used to treat or diagnose patients, i.e., not for investigational use, 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.



**50. 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 shipped or sold each year, and if that number exceeds 4,000, to provide an explanation and estimate to FDA of how the device is being used by patients. See 21 CFR 814.126(b)(1)(iii). Similarly, it is the responsibility of the HDE holder whose HUDs are approved by FDA to make a profit to monitor when the number of devices shipped or sold each year exceeds the ADN. For more on exceeding the ADN, see question 23.

**51. Must an IRB review or audit the medical records of patients who received a HUD?**

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

**52. 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.

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

HDE holders may generally charge for the HUD that is used to treat or diagnose a patient. However, unless FDA determines that the HUD qualifies for an exception, HUDs cannot be sold for a price that exceeds the costs of research and development, fabrication, and distribution of the device. FDA may determine that the HDE-approved HUD may be sold for profit if the HUD is (i) indicated and labeled for use in a pediatric population or pediatric subpopulation, or (ii) intended for the treatment or diagnosis of a disease or condition that does not occur in pediatric patients or that occurs in pediatric patients in such numbers that the development of the device for such patients is impossible, highly impracticable, or unsafe, and annual distribution of HUDs has not yet exceeded the ADN (as discussed in "Eligibility for Profit" section above). See section 520(m)(4), (6) of the FD&C Act.

If a HUD is studied in a clinical investigation for a new indication, the sponsor of the clinical investigation cannot charge subjects or investigators a price higher than necessary to recover the costs of manufacture, research, development, and handling (21 CFR 812.7(b)). Any costs for which a subject in a clinical investigation is responsible must, when appropriate, be provided in the informed consent document (21 CFR 50.25(b)(3)).

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

No. The IRB may, however, ask the HDE holder for copies of the safety information submitted to FDA in the periodic reports required by 21 CFR 814.126(b)(1). In this way,

information that could have a bearing on human safety would be considered at the time of continuing review.

**55. Do the requirements for review of a HUD change if an IRB has a Federal Wide Assurance (FWA) with the Department of Health and Human Services, Office for Human Research Protections?**

No. The use of a HUD is not research; rather, it is use of a legally marketed device. If, however, a HUD is used in a clinical investigation (see question 39), IRBs should follow their FWA requirements and their written procedures for FDA-regulated research.

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

Neither the FD&C Act nor the regulations require informed consent from patients for the use of a HUD for its HDE-approved indication(s). 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.fda.gov/medicaldevices/productsandmedicalprocedures/deviceapprovalsandclearances/hdeapprovals/ucm161827.htm> 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.

For discussion of physician interactions with patients in emergency use situations, see question 61.

**57. 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. You should also include information reflecting the HUD status of the device, such as a sentence indicating that 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.

**58. Is it appropriate for the HUD labeling and materials to include the phrase “FDA approved”? What other information must the labeling contain?**

Yes, the HUD labeling and materials may include the phrase “FDA approved.” However, HUD labeling and materials must be truthful and not misleading. See section 502(a) of the FD&C Act. Therefore, the labeling must also include the following statement clarifying that effectiveness has not been demonstrated: “Humanitarian Device. Authorized by Federal law for use in the [treatment or diagnosis] of [specify disease or condition]. The effectiveness of this device for this use has not been demonstrated.” See 21 CFR 814.104(b)(4)(ii) for more information on HUD labeling requirements.

**59. 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 40). Physicians may be either the sponsor or investigator of the study. 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.

## **Using HUDs in Emergency Use Situations**

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

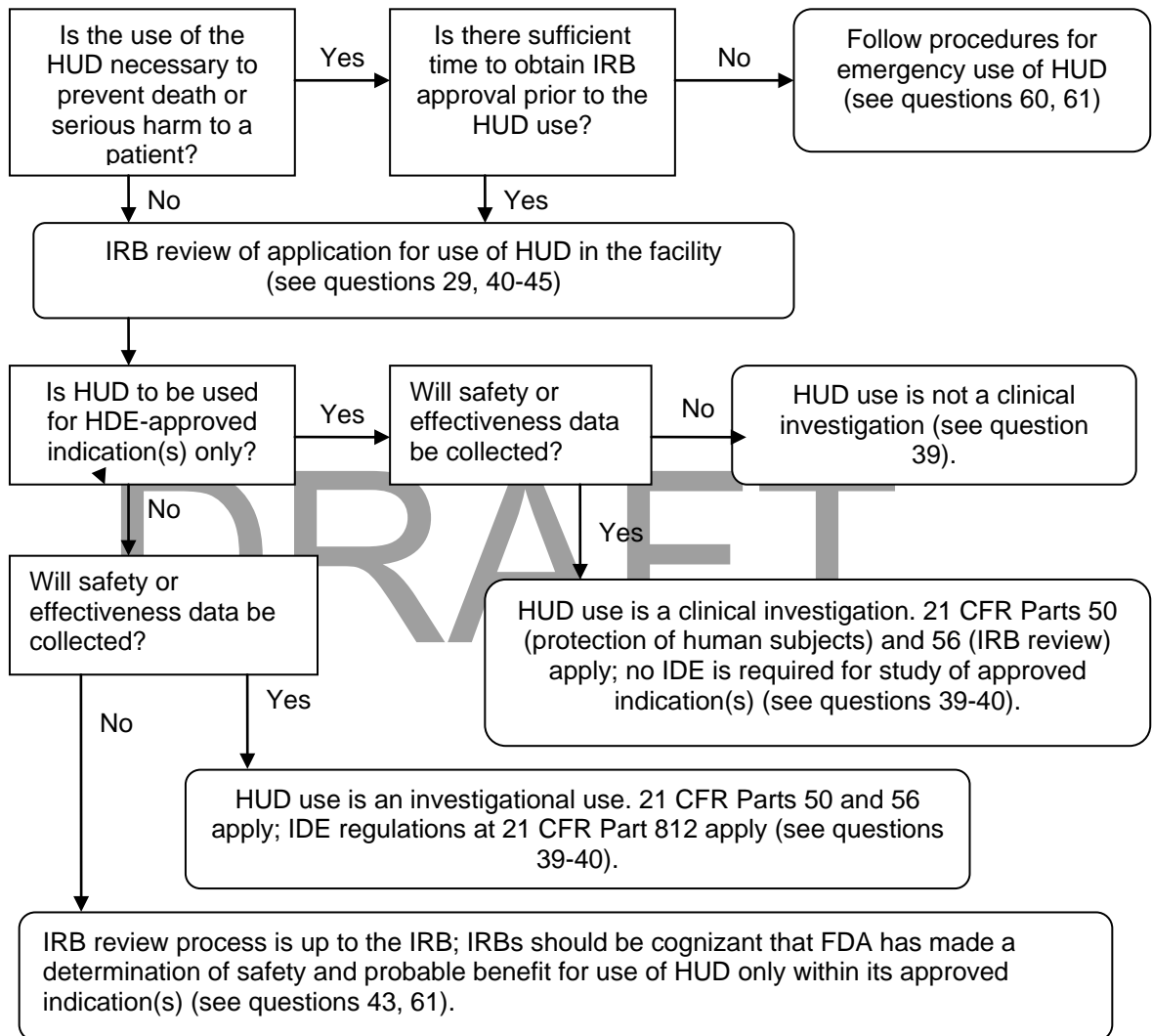
If a physician in an emergency situation determines that IRB approval for the use of the HUD at the facility cannot be obtained in time to prevent serious harm or death to a patient, a HUD may be used without prior IRB approval. The physician must, within 5 days after the emergency use of the device, provide written notification of the use to the IRB chair person. The written notification must include the identification of the patient involved, the date of the use, and the reason for the use. See section 520(m)(4) of the FD&C Act; 21 CFR 814.124.

**61. 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?**

Physicians should be cognizant that FDA has made a determination of safety and probable benefit for use of a HUD approved under an HDE only within its approved indication(s). If a physician wants to use a HUD 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 and first check with the IRB before such use to review any institutional policy. The extent of IRB oversight in these circumstances is up to the IRB (see questions 43 and 44). Note: as discussed in question 31, MDR reports must be submitted to FDA and to the “IRB of record” (i.e., the IRB approving the use of the HUD) if the device may have caused or contributed to death or serious injury and for certain malfunctions.

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**Figure 1: Decision Tree for IRB Review of HUDs**



Note: Medical device reporting is required under 21 CFR Part 803 whenever the use of 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 (see question 31). For investigational use of a HUD under an IDE, reports of unanticipated adverse device effects must be reported under 21 CFR 812.150(a)(1) and 812.150(b)(1).

**64. Flowchart.**

- Is the HUD use necessary to prevent death or serious harm to a patient?
  - If no, proceed to node 1; if yes, is there sufficient time to obtain IRB approval prior to the HUD use?
  - If yes, proceed to node 1; if no, Follow procedures for emergency use of HUD (see questions 60, 61).
- Node 1, IRB review of application for use of HUD in the facility (see questions 29, 40-45). Is HUD to be used for HDE-approved indication(s) only?
  - If no, proceed to node 2.
  - If yes, will safety or effectiveness data be collected?
    - If yes, HUD use is a clinical investigation. 21 CFR Parts 50 (protection of human subjects) and 56 (IRB review) apply; no IDE is required for study of approved indication(s) (see questions 39-40).
    - If no, HUD use is not a clinical investigation (see question 39).
- Node 2, will safety or effectiveness data be collected?
  - If yes, HUD use is a clinical investigation. 21 CFR Parts 50 and 56 apply; IDE regulations at 21 CFR Part 812 apply (see questions 39-40).
  - If no, IRB review process is up to the IRB; IRBs should be cognizant that FDA has made a determination of safety and probable benefit for use of HUD only within its approved indication(s) (see questions 43, 61).

*Contains Nonbinding Recommendations*

*Draft – Not for Implementation*

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