HDE Indication
For use in the treatment of free perforation - defined as free contrast extravasation into the pericardium, in native coronary vessels or saphenous vein bypass grafts ≥ 2.75 mm in diameter. IRB Approval Required for Use.
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Introduction:

The GraftMaster® RX Coronary Stent Graft System is approved under a Humanitarian Device Exemption (HDE) only for the treatment of free perforations, defined as free contrast extravasation into the pericardium, in native coronary vessels or saphenous vein bypass grafts ≥ 2.75 mm in diameter. The effectiveness of this device for this use has not been demonstrated. Long-term outcome for this permanent implant is unknown at present.

This Institutional Review Board (IRB) Booklet is intended to provide a high level understanding of the process and documentation requirements for using the GraftMaster® RX Coronary Stent Graft System product in compliance with HDE regulations and FDA guidance.

Regulations:

HUD Regulations and Federal Guidance

HUDs are approved devices whose use must comply with 21 CFR 814, Subpart H "Humanitarian Use Devices," and 21 CFR Part 803, "Medical Device Reporting." Federal Regulation 21 CFR 814.124 requires IRB review and approval of the use of the device, even though the use does not constitute research. The following is an excerpt from current FDA guidance entitled, Guidance for HDE Holders, Institutional Review Boards (IRBs), Clinical Investigators, and Food and Drug Administration Staff - Humanitarian Device Exemption (HDE) Regulation: Questions and Answers, Document Issued on July 8, 2010 and explains the requirements for IRB review:

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 in FDA guidance). 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(s)). 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 21 CFR Part 56 (21 CFR 814.124(a)). See question 46 (FDA guidance) for further discussion of the scope of the IRB approval.
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).

Update regarding Compassionate Use

Regarding compassionate use, FDA no longer requires obtaining their approval prior to compassionate use. This recommendation has been removed from the guidance and Abbott Vascular has been informed by FDA that obtaining FDA approval prior to each compassionate use is no longer recommended.

General Information

Examples of documentation that will be required from physicians and/or IRBs seeking to use or allow the use of the GraftMaster at their facilities are also provided for reference.

This booklet also contains Abbott Vascular’s relevant documentation of FDA’s approval of the GraftMaster® RX Coronary Stent Graft System under the HDE regulations.

For additional questions, please contact usgraftmasterhud@av.abbott.com
21 CFR 814.124 Institutional Review Board Requirements

(a) **IRB approval.** The HDE holder is responsible for ensuring that a HUD approved under this subpart is administered only in facilities having an Institutional Review Board (IRB) constituted and acting pursuant to part 56 of this chapter, including continuing review of use of the device. In addition, a HUD may be administered only if such use has been approved by the IRB located at the facility or by a similarly constituted IRB that has agreed to oversee such use and to which the local IRB has deferred in a letter to the HDE holder, signed by the IRB chair or an authorized designee. If, however, a physician in an emergency situation determines that approval from an IRB cannot be obtained in time to prevent serious harm or death to a patient, a HUD may be administered without prior approval by the IRB located at the facility or by a similarly constituted IRB that has agreed to oversee such use. In such an emergency situation, the physician shall, within 5 days after the use of the device, provide written notification to the chairman of the IRB of such use. Such written notification shall include the identification of the patient involved, the date on which the device was used, and the reason for the use.

(b) **Withdrawal of IRB approval.** A holder of an approved HDE shall notify FDA of any withdrawal of approval for the use of a HUD by a reviewing IRB within 5 working days after being notified of the withdrawal of approval.
Guidance for HDE Holders, Institutional Review Boards (IRBs), Clinical Investigators, and Food and Drug Administration Staff

Humanitarian Device Exemption (HDE) Regulation: Questions and Answers

Document issued on: July 8, 2010


The draft of this document was issued on August 5, 2008

OMB control number: 0910-0661
Expiration Date: 05/31/2013
See additional PRA statement in Section 67 of this guidance

For questions regarding this document, contact Sheila Brown, CDRH, at (301) 796-6563 or sheila.brown@fda.hhs.gov or the Office of Communication, Outreach and Development (CBER) at 1-800-835-4709 or 301-827-1800.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Office of Device Evaluation
Program Operations Staff
Center for Biological Evaluation and Research
Contains Nonbinding Recommendations
Preface

Public Comment

Written comments and suggestions may be submitted at any time for Agency consideration to the Division of Dockets Management, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD, 20852. Alternatively, electronic comments may be submitted to http://www.regulations.gov. When submitting comments, please refer to Docket No. FDA-2008-D-0434. Comments may not be acted upon by the Agency until the document is next revised or updated.

Additional Copies

Additional copies are available from the Center for Devices and Radiological Health (CDRH) through the Internet at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocument s/ucm110194.htm You may also send an e-mail request to dsmica@fda.hhs.gov to receive an electronic copy of the guidance document or send a fax request to 301-847-8149 to receive a hard copy. Please use the document number (1668) to identify the guidance document you are requesting.

Additional copies of this guidance document are also available from the Center for Biologics Evaluation and Research (CBER), Office of Communication, Outreach and Development (HFM-40), 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, or by calling 1-800-835-4709 or 301-827-1800, or from the Internet at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/default.htm.
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Guidance for HDE Holders, Institutional Review Boards (IRBs), Clinical Investigators, and FDA Staff

Humanitarian Device Exemption (HDE) Regulation: Questions and Answers

This guidance represents the Food and Drug Administration's (FDA’s) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

Introduction

This guidance document 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 guidance document reflects the additional requirements set forth in the Pediatric Medical Device Safety and Improvement Act of 2007.

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.

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.
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. Who is an HDE holder?

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

4. What does it mean to “use” a HUD?

The term “use” in this document, when unmodified, refer to the use of a HUD according to its approved labeling and indication(s) to treat or diagnose patients. When a HUD is being used in a clinical investigation (i.e., collection of safety and effectiveness data), the terms “investigational use” or “clinical investigation” will be used. A HUD may be studied in a clinical investigation in accordance with its approved indication(s) for a different indication, subject to the requirements described below. For more information on "use" versus "investigational use"/"clinical investigation" of a HUD, see questions 40-42 and "Figure 1: Decision Tree for IRB Review of HUDs" at the end of this guidance.

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 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 and
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 additional information on each of the above items.

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

After all supportive materials have been received along with the applicant’s request for HUD designation, we 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 (US) per year. In the case of a device used for diagnostic purposes, we also determine at that time whether the documentation demonstrates that fewer than 4,000 individuals per year would be subjected to diagnosis by the device in the United States (21 CFR 814.102(a)(5)).

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 affected, or in which the disease or condition is manifested, is less than 4,000 per year in the US. In the case of a device used for diagnostic purposes, it may also still qualify for HUD designation despite there being multiple contacts with the device by a single patient; the documentation must demonstrate that fewer than 4,000 individuals per year would be subjected to diagnosis by the device in the United States (21 CFR 814.102(a)(5)). That is, devices used in 4,000 or more patients a year to diagnose a subpopulation of less than 4,000 patients with a disease or condition would not be eligible for HUD designation (21 CFR 814.102(b)(3)(ii)).

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 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 approve 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)
Food and Drug Administration
WO32-5271

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.
10903 New Hampshire Avenue
Silver Spring, Maryland 20993-0002

If you have questions about the HUD designation, FDA’s Office of Orphan Products Development is available at (301) 796-8660.

12. Where do I submit an HDE application?

Submit 6 copies\(^2\) of your 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 Mail Center – WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002.

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 approve or deny an HDE application under 21 CFR 814.114. 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?

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, however, 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). For example, an HDE supplement does not warrant eligibility for profit if the HDE was previously approved before September 27, 2007, 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 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. 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, 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 approves 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 4,000, then this number is the ADN. If the number calculated is equal to or more than 4,000, then the ADN is capped at 3,999 because the ADN must be less than 4,000 devices. See section 520(m)(6)(A)(ii) of the Act.

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 approved.

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, the ADN must be less than 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 31): 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.

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.
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 are not subject to the ADN reporting requirement. The ADN relates only to those devices that are on the market through the HDE process for a disease or condition that occurs in pediatric patients or in a pediatric subpopulation. In that instance, the manufacturer is only required to notify FDA when sales or shipments tracked pursuant to the HDE exceed the ADN.

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 HUDs 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 agency exempts from the prohibition on profit. Once the HDE holder notifies the agency, or once the agency discovers through an inspection, that the ADN 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.”

**After FDA Approves an HDE**

**27. 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.

**28. 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 prohibition on profit. See section 520(m)(3) of the Act; 21 CFR 814.104(b)(5). As explained in the “HDEs and Pediatric Patients” section above, however, some HUDs are 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.

For devices that have both an HDE and a PMA approval for a different indication, there is no restriction on profit from sales pursuant to the PMA.

**29. 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. HDEs for pediatric use approved on or after September 27, 2007, are exempt from the prohibition against

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5. 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).
profiting from the sale of the device up to ADN, as explained in the "HDEs and Pediatric Patients" section above.

30. What adverse event reporting requirements apply to HUDs?

Device user facilities and manufacturers 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 sections 519(a) and (b) of the 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 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). Note: Pediatric adverse events will be reviewed periodically by the agency’s Pediatric Advisory Committee (http://www.fda.gov/oc/advisory/default.htm). The specific requirements for this reporting are set forth in the Medical Device Reporting (MDR) Regulation, at 21 CFR Part 803.

31. 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 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 only required to report 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. See 21 CFR 814.126(b)(1) for more information on these reports.
32. 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.

33. What happens to an approved HDE if, subsequently, FDA 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 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.

34. If a HUD is being investigated in an IDE study for a different indication, does it impact the number of allowable patients 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 United States 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.

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 that 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 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.

We remind IRBs that question 4 of this document makes a distinction between “use” of a HUD and “investigational use”/“clinical investigation” of a HUD. The term “use” in this document, when unmodified, refers to the use of a HUD according to its approved labeling and indication(s). If a HUD is being used in a clinical investigation (i.e., collection of safety and effectiveness data), whether for its HDE-approved indication(s) or for a different indication, then this document refers to “investigational use” or “clinical investigation” of the HUD. Such investigational use is subject to the same requirements that apply to all FDA-regulated clinical studies, including 21 CFR Parts 50 (Protection of Human Subjects) and 56 (Institutional Review Boards). Additionally, if the HUD is being studied for a use other than its approved indication(s), the IDE regulations at 21 CFR Part 812 apply. See questions 40-42.

For a schematic view of the difference between "use" and "investigational use"/"clinical investigation" of a HUD, please refer to “Figure 1: Decision Tree for IRB Review of HUDs” at the end of this guidance.

37. 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. As stated above, 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.

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. Once cleared, it can be marketed and sold in accordance with its labeling. There are no restrictions on the price, and it can be used by anyone qualified to use the device.

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 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 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. 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 the approval of an HDE application for a device, any studies conducted using the device must be under 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.

An HDE holder may collect safety and effectiveness data in a clinical investigation for the HDE-approved indication(s) without an IDE. As long as the HUD is being studied in accordance with the approved indication(s) described in labeling, the HUD, as such, is legally marketed and can be lawfully shipped without an IDE. See 21 CFR 812.1. IRB approval (21 CFR Part 56) and protection of human subjects (21 CFR Part 50) are still required for these studies because they are FDA-regulated clinical studies.

Clinical investigation of a HUD for a different indication must be conducted in compliance with the IDE regulations at 21 CFR Part 812, in addition to requiring IRB approval (21 CFR Part 56) and protection of human subjects (21 CFR Part 50). If the device is a significant risk device, an FDA-approved IDE is required. See 21 CFR 812.1, 812.20. To date, all HUDs have been significant risk devices requiring FDA-approved IDEs. See question 42 for more discussion of significant risk devices.

In short, IRB approval, informed consent, and additional safeguards for children (if applicable) are required for the clinical investigation (investigational use) of a HUD,
whether the HUD is being studied for its HDE-approved indication(s) or for a different indication. These requirements are separate and distinct from the requirements that apply to the use of a HUD at a facility: as described in questions 43 and 59, IRB approval is required before a HUD is used at a facility to treat or diagnose patients and the IRB may require informed consent as part of such approval. In other words, just because an IRB has approved use of a HUD at a facility to treat or diagnose patients does not mean that the IRB has approved investigational use of the HUD (i.e., in a clinical investigation), for the collection of safety and effectiveness data. For more information on the difference between "use" of a HUD and "investigational use"/"clinical investigation" of a HUD, see “Figure 1: Decision Tree for IRB Review of HUDs” at the end of this guidance.

40. What if the HDE holder decides to collect safety and effectiveness data in a study to support a PMA for the HDE-approved indications?

As stated above, you may collect safety and effectiveness data to support a PMA for the HDE-approved indication(s) without an IDE. While the work done to collect such safety and effectiveness data to support a PMA constitutes a clinical investigation, FDA considers the study exempt from the requirement for an IDE as long as the HUD is used in accordance with its approved indication(s). IRB approval (21 CFR Part 56) and protection of human subjects (21 CFR Part 50) are still needed, however, as required for all FDA-regulated clinical studies. As noted above, the IRB approval, informed consent, and additional safeguards for children (if applicable) required for the clinical investigation/investigational use of a HUD are separate and distinct from the IRB approval and any consent associated with the use of the HUD. That an IRB has approved use of a HUD at a facility to treat or diagnose patients does not mean the IRB has approved investigational use of the HUD (i.e., in a clinical investigation), for the collection of safety and effectiveness data.

If you want to collect safety and effectiveness data for a use other than the HDE-approved indication(s), you must comply with the IDE regulations at 21 CFR Part 812 in addition to complying with the requirements for IRB approval (21 CFR Part 56) and protection of human subjects (21 CFR Part 50).

41. 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 use of a HUD at a facility (see questions 43-52), its review does not include an SR/NSR determination. As noted above, use of a HUD at a facility to treat or diagnose patients is not a "clinical investigation"; the HUD as such is legally marketed for use within its HDE-approved indication(s).

If an IRB receives a request to review a clinical investigation of a HUD (i.e., collection of safety and effectiveness data), and that clinical investigation concerns the HDE-approved indication(s), then again the IRB does not have to make an SR/NSR determination in its review. FDA considers such investigations exempt from the IDE
requirements in 21 CFR Part 812, as noted above. Nonetheless, the IRB still has to approve the clinical investigation under 21 CFR Part 56 and 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 HDE for a different indication, then the IRB should be alert that this type of clinical investigation is subject to the IDE regulations at 21 CFR Part 812. To date, all HUDs when 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, and so IRBs have not needed to make the SR/NSR determination (i.e., the sponsors already knew their device was an 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 described in 21 CFR 812.66.

42. 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 21 CFR Part 56 (21 CFR 814.124(a)). See question 46 for further discussion of the scope of IRB approval.

43. 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.

44. 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 initial and 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, ensure the risks are minimized, and evaluate whether 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.

45. 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.

46. 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.

47. 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.

48. 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 risk posed by the technology or software compatibility may supplement the IRB review.

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

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) shall also be submitted to the "IRB of record" (i.e., the IRB approving the use of the HUD).

50. 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).

51. 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 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.

52. 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).

53. 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.

54. 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.

55. 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. The exception is 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 indication, 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 a subject in a clinical investigation is responsible must when appropriate, be clearly explained in the informed consent document (21 CFR 50.25(b)(3)).

56. 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.

57. 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. We describe the IRBs responsibilities in section 520(m) of the Act 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.

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

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).

59. 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.

60. 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 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.

61. 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 42). 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.

62. **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.

63. **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)?**

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**
64. 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.

65. 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 the HUD 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 question 46). 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.
Figure 1: Decision Tree for IRB Review of HUDs

- Is the HUD use necessary to prevent death or serious harm to a patient?
  - Yes
  - No

- Is there sufficient time to obtain IRB approval prior to the HUD use?
  - Yes
  - No

- Follow procedures for emergency use of HUD (see questions 64, 65)

- IRB review of application for use of HUD in the facility (see questions 41-47)

- Is HUD to be used for HDE-approved indication(s) only?
  - Yes
  - No

- Will safety or effectiveness data be collected?
  - Yes
  - No

- 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 39-41).

- Is HUD being used as part of a clinical investigation?
  - Yes
  - No

- HUD use is a clinical investigation. 21 CFR Parts 50 and 56 apply; IDE regulations at 21 CFR Part 812 apply (see questions 39-41).

- 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 45,65).

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 questions 30, 49, 65). 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).
Section 508 text for Figure 1.

**66. 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 64, 65). Node 1, IRB review of application for use of HUD in the facility (see questions 41-47). 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 39-41). If no, HUD use is not a clinical investigation (see question 39). Node 2, is HUD being used as part of a clinical investigation? 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 39-41). 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 45, 65).

**67. Paperwork Reduction Act of 1995**

This guidance contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520). The time required to complete this information collection is estimated to average 100 hours per response, including the time to review instructions, search existing data sources, gather the data needed, and complete and review the information collection. Send comments regarding this burden estimate or suggestions for reducing this burden to:

U.S. Food and Drug Administration
Center for Devices and Radiological Health
HDE Program WO66-1645
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
This guidance also refers to previously approved collections of information found in FDA regulations. The collections of information in 21 CFR part 803 have been approved under OMB control number 0910-0437; the collections of information in 21 CFR part 812 have been approved under OMB control number 0910-0078; the collections of information in 21 CFR part 807, subpart E have been approved under OMB control number 0910-0120; the collections of information in 21 CFR part 814, subparts A, B, and C have been approved under OMB control number 0910-0231; the collections of information in 21 CFR parts 50 and 56 have been approved under OMB control number 0910-0130; the collections of information in 21 CFR part 820 have been approved under OMB control number 0910-0073; the collections of information in 21 CFR part 814, subpart H have been approved under OMB control number 0910-0332; and the collections of information in 21 CFR 10.30 have been approved under OMB control number 0910-0183.

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. The OMB control number for this information collection is 0910-0661, which expires on 05/31/2013.
To qualify a case under the compassionate use regulations, the patient shall meet the following two criteria:

- Serious disease or condition (non-emergency)
- No generally acceptable alternative treatment for the condition exists.

**IRB Approval prior to Compassionate Use** – Site Institutional Review Board should decide whether they want to approve Off Label Compassionate Use of the HUD or Not.

The following documents must be provided to Abbott Vascular (AV) for compassionate use.

1. A letter to AV requesting approval for using off-label on a compassionate basis. The letter shall include:
   a) a description of the patient’s condition and the circumstances necessitating treatment,
   b) a discussion of why alternative therapies are unsatisfactory, or
   c) that no other alternative treatments are available.

2. An independent assessment from an uninvolved physician.

3. Concurrence of the IRB chairperson.

4. Clearance from the institution as specified by their policies.

5. Informed consent from the patient or his/her legal representative (patient must be informed of the “off-label” use of the device and consent must be documented. AV has a template IC (FRM5831-01GraftMaster® Informed Consent Form).

When AV Regulatory Affairs receives the above items, AV will in turn forward the acknowledge receipt notification to the original requester.

**After-use Procedures**

Upon completion of the case, the physician must provide the following items by fax to AV Regulatory Affairs at (408) 845-2550:

1. Completed GraftMaster® Device Registration Form PPL2082234)
2. Cath Report and “follow-up” paragraph from the physician stating the outcome of the procedure and outlining the plan for monitoring the patient, taking into consideration the limited information available regarding the potential risks and benefits of the device and the specific needs of the patient. Abbott Vascular will include the case in the FDA Annual Report.

Reference: 21 CFR 812.35(a)

http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm110194.htm
In an emergency situation, GraftMaster® may be used off-label (i.e. outside its approved indications for use) to save the life or protect the physical well-being of a patient, (per FDA Guidance for Humanitarian Device Exemptions (HDE) Regulation: Questions and Answers http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm110194.htm

To qualify a case under Emergency Use, a patient shall meet the following criteria:

1. The patient has a life-threatening condition that needs immediate treatment.
2. No generally acceptable alternative treatment for the condition exists; and
3. Because of the immediate need to use the device, there is no time to use existing procedures to obtain prior IRB (Institutional Review Board) approval for the use.

FDA expects the physician to make the determination that the patient’s circumstances meet the above criteria, to assess the potential for benefit from the use of the unapproved device, and to have substantial reason to believe that benefits will exist. In the event that a device is used in circumstances meeting the criteria listed above, the physician shall follow as many patient protection procedures as possible.

After-use Procedures
After the emergency use of the GraftMaster® occurs, the physician must submit the following documents by fax to Abbott Vascular Regulatory Affairs at (408) 845-2550:

1. Completed GraftMaster® Device Registration Form (PPL2082234) signed & dated.
2. Patient Information and the patient protection measures that were followed (FRM5831-02). Patient shall be informed of the “off-label” use of the device and this piece of information needs to be documented.
3. Concurrence/Acknowledgement of the IRB chairperson (FRM5831-03).
4. Clearance from the institution as specified by their policies.
5. An independent assessment from an uninvolved physician.
6. Cath Report/Procedure report - detailing the implant of GraftMaster®, outcome, and any follow up that is now required, if application.

The physician must notify Abbott Vascular within 48 hours after the procedure and provide the required documentation. Abbott Vascular will include the case in the FDA annual report on the HDE.
Dear IRB Chairperson:

The purpose of this letter is to provide notification to the IRB of our intention to begin clinical use of a Humanitarian Use Device for the treatment of coronary artery perforations. FDA has approved both the GraftMaster® RX Coronary Stent Graft System and JOSTENT GraftMaster® OTW Coronary Stent Graft System (hereinafter, referred to as GraftMaster®) for commercial use in selected patients under a Humanitarian Device Exemption (HDE). Specifically, the GraftMaster® Coronary Stent Graft System has been approved for use in the treatment of free perforations, defined as free contrast extravasation into the pericardium, in native vessels or saphenous vein bypass grafts greater than or equal to ≥2.75 mm in diameter. The effectiveness of this device for this use has not been demonstrated. Long-term outcome for this permanent implant is unknown at present.

A Humanitarian Device Exemption (HDE) approval is an alternative approval process established by the FDA in order to provide a mechanism for commercial development and approval of new device technologies that may benefit small patient population groups (<4000 patients in the United States are affected each year). FDA grants commercial approval for such devices after a review of safety data gathered from pre-clinical testing and clinical use of the product for the specific indication. Additionally, limited efficacy data was provided to the FDA for their review. FDA concluded from the data that the probable benefits of the device outweigh the probable risks for this indication.

Unlike other commercially available devices, under HDE regulations, the product may only be used by or on the order of a physician or other licensed practitioner in facilities that have IRB approval to use the device. Under the HDE regulations, physicians intending to use the product must inform their IRB of their plans to do so. As this device is commercially approved under HDE, there is no investigational protocol to follow nor is use of the device considered “research.” As we intend to begin using the GraftMaster® Coronary Stent Graft System in selected patients as indicated above, we will need approval from the IRB to initiate use of the device.
More information on the IRB’s role with respect to the Humanitarian Device regulations is available on FDA’s website at [http://www.fda.gov/oc/ohrt/irbs/irbchecklist.html](http://www.fda.gov/oc/ohrt/irbs/irbchecklist.html).

As per FDA regulations regarding Humanitarian Use Devices, IRB approval of the use of the device is required before we can use it. Again, please note that the device has been approved by FDA and no longer requires that a clinical research protocol be followed. However, my intention is to follow these patients in a departmental registry, similar to that used for our patients implanted with other cardiac implants. I will provide the IRB with an annual report specifying GraftMaster® Coronary Stent Graft System use and results. In addition, I will notify the IRB if there are any unanticipated adverse events related to use of the device. Thus, in accordance with the regulations, I am requesting that the committee provide me a letter authorizing the use of the device for this indication. Abbott Vascular requires this letter as well in order to comply with the HDE regulations. The letter needs to specify use of the GraftMaster® Coronary Stent Graft System for the treatment of free perforation, defined as free contrast extravasation into the pericardium, in native coronary vessels or saphenous vein bypass grafts ≥ 2.75 mm in diameter. The approval letter needs to be issued on a facility letterhead. It should indicate whether the review was an initial review or continuing review, and whether the approval was granted by the full board or via an expedited review. The letter should also specify the approval date, the expiration date, and name and address of each facility covered under this authorization letter. Please refer to the following page for a sample IRB approval letter.

In addition to the IRB approval mentioned above, physicians who intend to use the GraftMaster® Coronary Stent Graft System will receive an in-service training provided by Abbott Vascular. In-service arrangements will be made with AV after receipt of the approval letter.

I look forward to your prompt attention to this matter. Should the IRB committee have any questions, please feel free to contact me. I would be happy to attend the IRB committee meeting to answer any questions the members may have.

Sincerely,

[Insert Dr. Name & Title here]

Attachments
Re: Use of GraftMaster® Coronary Stent Graft System for the treatment of free perforations, defined as free contrast extravasation into the pericardium, in native coronary vessels or saphenous vein bypass grafts ≥ 2.75 mm in diameter. The effectiveness of this device for this use has not been demonstrated. Long-term outcome for this permanent implant is unknown at present.

Approval Date: <Date>
Expiration Date: <Date>

Note: Please note for initial approval (first time), IRBs are required to perform their review at a convened meeting (21 CFR 56.108). IRB’s must review & reapprove annually (expiration dates can’t exceed 12 months). Please forward the renewal letter to usgraftmasterhud@av.abbott.com or fax 408-845-2550.

Dear <Dr. >:

The Institutional Review Board of <Facility> met on <date>. This is to confirm that the Committee approved the use of GraftMaster® Coronary Stent Graft System under a Humanitarian Device Exemption in the following hospitals:

- <Name of Site #1>
  <Address of Site #1>

- <Name of Site #2, if applicable>
  <Address of Site #2>

- <Name of Site #3, if applicable>
  <Address of Site #3>

<Name of IRB Contact>
<Phone Number of IRB Contact>
<Email for IRB Contact>
<Protocols/procedures from the IRB may appear here>

Sincerely,

<Signature of IRB Chairperson>
<Name of IRB Chairperson>
<Email of IRB Chairperson>
IRB Approval Letter Fax Cover Sheet

To: Regulatory Affairs
Email /Fax#: usgraftmasterhud@av.abbott.com
(408) 845-2550*
*Only fax when email isn’t an option

From: ____________________________
Phone#: ____________________________
Fax#: ____________________________
Total # of Pages: (including this page) _____________
Sales Rep: ____________________________
Abbott Customer#: ____________________________
Hospital covered under the IRB Approval: ____________________________
Hospital Address: ____________________________

Additional Hospitals covered under the same IRB Approval: ____________________________

Any order in System? ____________________________

Comments
______________________________________________________________________________
______________________________________________________________________________

38
Abbott Vascular Customer Service

To Purchase the GraftMaster® RX Coronary Stent Graft System

- 24/7 Customer Support - Live personnel available any time of the day or night for emergency after hours support
- Phone: 1-800-227-9902
- Fax: 1-800-601-8874
- Email: av.customercare@av.abbott.com
- E-commerce: multiple options available (GHX and EDI)

Mr. Glenn N. Byrd  
Director, Regulatory Affairs  
Eminent Research Systems, Inc.  
c/o JOMED AB  
1700 Rockville Pike, Suite 400  
Rockville, MD 20852  

Re: HDE Number H000001  
JOMED JOSTENT® Coronary Stent Graft  
Filed: February 7, 2000  
Amended: March 23, September 7, October 27, October 27,  
December 13, December 19, 2000, and January 9, 2001  

Dear Mr. Byrd:  

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your humanitarian device exemption (HDE) application for the JOMED JOSTENT® Coronary Stent Graft. This device is indicated for use in the treatment of free perforations, defined as free contrast extravasation into the pericardium, in native coronary vessels or saphenous vein bypass grafts ≥ 2.75 mm in diameter. CDRH is pleased to inform you that your HDE is approved subject to the enclosed "Conditions of Approval." You may begin commercial distribution of the device after you have submitted an amendment to this HDE with copies of the approved labeling in final printed form.  

The sale, distribution, and use of this device are limited to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. In addition, in order to ensure the safe use of the device, FDA has further restricted the device within the meaning of section 520(e) of the act under the authority of section 515(d)(1)(B)(ii) of the act insofar as (1) the labeling shall specify the training requirements for practitioners who may use the device as approved in this order and (2) the sale, distribution, and use must not violate sections 502(q) and (r) of the act.  

FDA wishes to remind you that failure to comply with the conditions of approval invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.
CDRH will notify the public of its decision to approve your HDE by making available a summary of the safety and probable benefit of the device upon which the approval was based. The information can be found on the FDA CDRH Internet HomePage located at http://www.fda.gov/cdrh/ode/hdeinfo.html. Written requests for this information can also be made to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. The written request should include the HDE number or docket number. Within 30 days from the date that this information is placed on the Internet, any interested person may seek review of this decision by requesting an opportunity for administrative review, either through a hearing or review by an independent advisory committee, under section 515(g) of the act.

You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this HDE submission with copies of all approved labeling in final printed form. As part of our reengineering effort, the Office of Device Evaluation is piloting a new process for review of final printed labeling. The labeling will not routinely be reviewed by FDA staff when HDE applicants include with their submission of the final printed labeling a cover letter stating that the final printed labeling is identical to the labeling approved in draft form. If the final printed labeling is not identical, any changes from the final draft labeling should be highlighted and explained in the amendment. Please see the CDRH Pilot for Review of Final Printed Labeling document at http://www.fda.gov/cdrh/pmat/pilotpmat.html for further details.

Any information to be submitted to FDA regarding this HDE should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above HDE number to facilitate processing:

Document Mail Center (HFZ-401)
Office of Device Evaluation
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850
If you have any questions concerning this approval order, please contact H. Semih Oktay, Ph.D., at (301) 443-8243.

Sincerely yours,

Kimber C. Richter

Kimber C. Richter, M.D.
Deputy Director for Clinical Review Policy
Office of Device Evaluation
Center for Devices and Radiological Health

Enclosure
CONDITIONS OF APPROVAL FOR AN HDE

I. APPROVED LABELING

As soon as possible and before commercial distribution of the device, the holder of an HDE should submit three copies of the approved labeling in final printed form as an amendment to the HDE. The supplement should be submitted to the Document Mail Center (HFZ-401), Office of Device Evaluation, Center for Devices and Radiological Health, Food and Drug Administration (FDA), 9200 Corporate Blvd., Rockville, Maryland 20850.

II. ADVERTISEMENTS

Advertisements and other descriptive printed materials issued by the HDE holder or private label distributor with respect to this device should not recommend or imply that the device may be used for any use that is not included in the FDA approved labeling for the device. If the FDA approval order has restricted the sale, distribution and use of the device to prescription use in accordance with 21 CFR 801.109 and specified that this restriction is being imposed in accordance with the provisions of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 360j(e)) under the authority of section 515(d)(1)(B)(ii) of the act (21 U.S.C. 360e(d)(1)(B)(ii)), all advertisements and other descriptive printed material issued by the holder or distributor with respect to the device shall include a brief statement of the intended uses of the device and relevant warnings, precautions, side effects, and contraindications.

III. HDE SUPPLEMENTS

Before making any change affecting the safety or probable benefit of the device, the HDE holder should submit a supplement for review and approval by FDA unless a "Special HDE Supplement" is permitted as described under 21 CFR 814.39(d)(2) or an alternate submission is permitted as described under 21 CFR 814.39(e). All HDE supplements or alternate submissions must comply with the applicable requirements under 21 CFR 814.39 of the Premarket Approval (PMA) regulation and under 21 CFR 814.108 of the Humanitarian Device Exemption regulation. The review timeframe for HDE supplements is 75 days except for those submitted under 21 CFR 814.39(e).

Since all situations which require an HDE supplement cannot be briefly summarized, please consult the HDE regulation for further guidance. The guidance provided below is only for several key instances. In general, an HDE supplement must be submitted:

1) When unanticipated adverse effects, increases in the incidence of anticipated adverse effects, or device failures necessitate a labeling, manufacturing, or device modification; or

2) If the device is to be modified, and animal/laboratory or clinical testing is needed to determine if the modified device remains safe and continues to provide probable benefit.

HDE supplements submitted under 21 CFR 814.39(d)(2) "Special HDE Supplement - Changes Being Effected" are limited to the labeling, quality control, and manufacturing process changes as specified under this section of the regulation. This provision allows for the addition of, but not the replacement of previously approved, quality control specifications and test methods.
These changes may be implemented upon acknowledgment by FDA that the submission is being processed as a "Special HDE Supplement - Changes Being Effected." Please note that this acknowledgment is in addition to that issued by the Document Mail Center for all HDE supplements submitted. This procedure is not applicable to changes in device design, composition, specifications, circuitry, software, or energy source.

Alternate submissions permitted under 21 CFR 814.39(e) apply to changes that otherwise require approval of an HDE supplement before implementation and include the use of a 30-day HDE supplement or periodic postapproval report. FDA must have previously indicated in an advisory opinion to the affected industry or in correspondence to the HDE holder that the alternate submission is permitted for the change. Before this can occur, FDA and the HDE holder must agree upon any needed testing, the testing protocol, the test results, the reporting format, the information to be reported, and the alternate submission to be used.

Please note that unlike the PMA process, a supplement may not be submitted for a new indication for use for a humanitarian use device (HUD). An HDE holder seeking a new indication for use for an HUD approved under the provisions of Subpart H of 21 CFR 814, must obtain a new designation of HUD status for the new indication for use and submit an original HDE application in accordance with §814.104. The application for the new indication for use may incorporate by reference any information or data previously submitted to the agency.

IV. POSTAPPROVAL RECORD KEEPING REQUIREMENTS
An HDE holder is required to maintain records of the names and addresses of the facilities to which the HUD has been shipped, correspondence with reviewing institutional review boards (IRBs), as well as any other information requested by a reviewing IRB or FDA.

V. POSTAPPROVAL REPORTING REQUIREMENTS Continued approval of the HDE is contingent upon the submission of postapproval reports required under 21 CFR 814.84 and 21 CFR 814.126.

A. ANNUAL REPORT
Annual reports should be submitted at intervals of 1 year from the date of approval of the original HDE. Reports for supplements approved under the original HDE should be included in the next and subsequent periodic reports for the original HDE unless otherwise specified in the approval order for the HDE supplement. Three copies identified as "Annual Report" and bearing the applicable HDE reference number are to be submitted to the HDE Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850. Reports should indicate the beginning and ending date of the period covered by the report and include the following information required by 21 CFR 814.126(b)(1):
1. An update of the information required under §814.102(a) in a separately bound volume;

2. An update of the information required under §814.104(b)(2), (b)(3), and (b)(5);

3. The number of devices that have been shipped or sold and, if the number shipped or sold exceeds 4,000, an explanation and estimate of the number of devices used per patient. If a single device is used on multiple patients, an estimate of the number of patients treated or diagnosed using the device together with an explanation of the basis for the estimate;

4. Information describing the applicant's clinical experience with the device. This shall include safety information that is known or reasonably should be known to the applicant, a summary of medical device reports made pursuant to 21 CFR 803, any data generated from postmarketing studies, and information (whether published or unpublished) that is known or reasonably expected to be known by the applicant that may affect an evaluation of the safety of the device or that may affect the statement of contraindications, warnings, precautions, and adverse reactions in the device labeling; and

5. A summary of any changes made to the device in accordance with supplements submitted under §814.108 and any changes required to be reported to FDA under §814.39(b).

B. ADVERSE REACTION AND DEVICE DEFECT REPORTING
As provided by 21 CFR 814.82(a)(9), FDA has determined that in order to provide continued reasonable assurance of the safety and probable benefit of the device, the holder shall submit three copies of a written report identified, as applicable, as an "Adverse Reaction Report" or "Device Defect Report" to the Document Mail Center (HFZ-401), Office of Device Evaluation, Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850. Such reports should be submitted within 10 days after the HDE holder receives or has knowledge of information concerning:

(1) A mixup of the device or its labeling with another article.

(2) Any adverse reaction, side effect, injury, toxicity, or sensitivity reaction that is attributable to the device and

   (a) has not been addressed by the device's labeling or

   (b) has been addressed by the device's labeling, but is occurring with unexpected severity or frequency.
(3) Any significant chemical, physical or other change or deterioration in the device or any failure of the device to meet the specifications established in the approved HDE that could not cause or contribute to death or serious injury but are not correctable by adjustments or other maintenance procedures described in the approved labeling. The report shall include a discussion of the HDE holder's assessment of the change, deterioration or failure and any proposed or implemented corrective action by the firm. When such events are correctable by adjustments or other maintenance procedures described in the approved labeling, all such events known to the holder shall be included in the "Annual Report" described under "Postapproval Reports" above unless otherwise specified in the conditions of approval for this HDE. This postapproval report shall appropriately categorize these events and include the number of reported and otherwise known instances of occurrence for each category during the reporting period. Additional information regarding the events discussed above shall be submitted by the HDE holder when determined by FDA to be necessary to provide continued reasonable assurance of the safety and probable benefit of the device for its intended use.

C. REPORTING UNDER THE MEDICAL DEVICE REPORTING REGULATION
The Medical Device Reporting regulation (MDR) (21 CFR 803) became effective on April 11, 1996 and requires that all manufacturers and importers of medical devices, including in vitro diagnostic devices, report to FDA whenever they receive or otherwise became aware of information that reasonably suggests that one of its marketed devices:

(1) may have caused or contributed to a death or serious injury; or

(2) has malfunctioned and that the device or any other device marketed by the manufacturer or importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

Events subject to reporting under the MDR regulation may also be subject to the above "Adverse Reaction and Device Defect Reporting" requirements. FDA has determined, however, that such duplicative reporting is unnecessary. Therefore, whenever an event involving a device is subject to reporting under both the MDR regulation and the "Adverse Reaction and Device Defect Reporting" requirements, the report should be submitted in compliance with Part 803 and identified with the HDE reference number to Food and Drug Administration, Center for Devices and Radiological Health, Medical Device Reporting, PO Box 3002, Rockville, Maryland 20847-3002. For questions regarding the MDR regulation, please call (301) 594-2735.

Events included in periodic reports to the HDE that have also been reported under the MDR regulation must be so identified in the periodic report to the HDE to prevent duplicative entry into FDA information systems.
Copies of the MDR regulation and FDA publications, entitled "An Overview of the Medical Device Reporting Regulation" and "Medical Device Reporting for Manufacturers," are available on the CDRH WWW Home Page (http://www.fda.gov/cdrh), through CDRH's Fact-on-Demand (FOD) at 800-899-0381 (FOD # 336, 1336, 509 and 987) or by written request to the address below or by telephoning 1-800-638-2041.

Division of Small Manufacturers Assistance (HFZ-220)
Center for Devices and Radiological Health
Food and Drug Administration
1350 Piccard Lane
Rockville, Maryland 20850
Mr. Kobby Dankwah  
Director, Regulatory Affairs  
Abbott Vascular Devices  
400 Saginaw Drive  
Redwood City, CA  94063  

Re:  H000001/A010  
    Jostent Coronary Stent Graft and Jostent GraftMaster and Delivery System OTW  
    Received: January 8, 2004  

Dear Mr. Dankwah:  

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) received your request for a change in ownership from JOMED, Inc. to Abbott Vascular Devices. We have changed our records accordingly. All previous regulatory requirements remain in effect and are now the responsibility of Abbott Vascular Devices.  

As requested, FDA will provide you a complete copy of the HDE under the fee schedule in 21 CFR 20.42 of FDA's public information regulations.  

Future correspondence concerning this application should reference the HDE number above and must be submitted to:  

HDE Document Mail Center (HFZ-401)  
Center for Devices and Radiological Health  
Food and Drug Administration  
9200 Corporate Blvd.  
Rockville, Maryland  20850
If you have any questions concerning this letter, please contact Ms. Carolyn Vaughan at 301-443-8243 x152.

Sincerely yours,

[Signature]

Bram D. Zuckerman, M.D.
Director
Division of Cardiovascular Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

cc: Mr. Jeff Anderson
Vice President, Regulatory and Clinical Affairs
JOMED, Inc.
15330 Avenue of Science, Suite 200
San Diego, CA 92128
Ms. Suzanne Redman  
Abbott Vascular, Inc.  
Regulatory Affairs  
26531 Ynez Road  
Temecula, CA 92591  

Re: H000001/S008  
#99-0047  
GraftMaster Coronary Stent Graft System  
Filed: October 9, 2013  
Amended: January 22, 2013

Dear Ms. Redman:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its evaluation of your humanitarian device exemption application (HDE) supplement, which requested approval for a change in delivery system, manufacturing site and revisions to the Instructions For Use (IFU). Based upon the information submitted, the HDE supplement is approved subject to the conditions described in the approval order for your original HDE. You may begin commercial distribution of the device as modified by your HDE supplement upon receipt of this letter.

Failure to comply with the conditions of approval as described in the approval order for the original HDE invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the Federal Food, Drug, and Cosmetic Act.

You are reminded that as soon as possible and before commercial distribution of your device you must submit an amendment to this HDE with copies of all approved labeling in final form. The labeling will not routinely be reviewed by FDA staff when HDE supplement applicants include with their submission of the final printed labeling a cover letter stating that the final printed labeling is identical to the labeling approved in draft form. If the final printed labeling is not identical, any changes from the final draft labeling should be highlighted and explained in the amendment.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and reference the above HDE number to facilitate processing. One of those three copies may be an electronic copy (eCopy), in an electronic format that FDA can process, review and archive (general information:}
http://www.fda.gov/MedicalDevice/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/ucm134508.htm; clinical and statistical data: 
http://www.fda.gov/MedicalDevice/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/ucm136377.htm).

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

If you have questions concerning this approval order, please contact Katharine Fronczak at katharine.fronczak@fda.hhs.gov at (301) 796-5560.

Sincerely yours,

Owen P. Faris -S

for Bram D. Zuckerman, M.D. 
Director 
Division of Cardiovascular Devices 
Office of Device Evaluation 
Center for Devices and Radiological Health
PLEASE PRINT LEGIBLY

Name of Hospital: ________________________________

Address: ______________________________________

City: __________________ State: __________ Zip: ______

Physician Name: ________________________________ Phone No: __________

Cath Lab Contact: ____________________________ Phone No: __________

Case Details:

Date of Procedure: __________ (month/day/year)

Patient Initials: ___________ Sex: M □ F □ Patient Date of Birth: ____________________ (month/day/year)

Approved Indication: □ Treatment of free perforation, defined as free contrast extravasation into the pericardium, in native coronary vessels or saphenous vein bypass grafts ≥ 2.75 mm in diameter.

Other than approved indication: □ If checked, describe case: __________________________

Location of the vessel treated: ______________________

Perforation Sealed: Yes □ No □ Stent Implanted: Yes □ No □

Comments: __________________________________

Procedure:

Did use of the GRAFTMASTER RX cause or contribute to complications or adverse events? Yes □ No □

If Yes, please describe: __________________________________

Did patient die? Yes □ No □

If Yes, please describe: __________________________________

Device Details:

Catalog No: __________________

Lot No: __________________

No. Implanted: __________________

Stent Length(s): __________________

Max Pressure Used: __________________

Please attach barcode label here. No more than one device per form.

Name (Print) __________________ Signature __________________ Date __________

AFTER COMPLETION, PLEASE FAX TO ABBOTT VASCULAR REGULATORY AFFAIRS: 408-845-2550

HIPAA Statement:

This statement is to certify that the information collected on this form will be used solely for the purpose of required FDA data reporting on the HDE approved GRAFTMASTER RX Coronary Stent Graft. This information will not be used or released for any other purpose. Per the HIPAA Privacy Regulations, Title 45 CFR Part 164.512 (b) (iii) (B), written authorization of the individual or the opportunity for the individual to agree or object is not required for disclosure of protected health information for FDA regulated products that are required to be tracked, such as the HDE approved GRAFTMASTER RX Coronary Stent Graft.

GRAFTMASTER is a registered trademark of the Abbott Group of Companies.

PPL2093098 (2/11/13)
Graphical Symbols for Medical Device Labeling

- **Manufacturer**
- **Catalogue number**
- **French size**
- **Do not reuse**
- **Consult instructions for use**
- **Date of manufacture**
- **Use by**
- **Do not re-sterilize**
- **Lot code**
- **Batch code**
- **Outer diameter**
- **Inner diameter**
- **Guiding catheter**
- **Contents (numeral represents quantity of units inside)**
- **Sterilized using ethylene oxide**
- **MR Conditional**
Humanitarian Device. Authorized by Federal law for use in the treatment of free perforations, defined as free contrast extravasation into the pericardium, in native coronary vessels or saphenous vein bypass grafts ≥ 2.75 mm in diameter. The effectiveness of this device for this use has not been demonstrated.

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1.0 DEVICE DESCRIPTION
The GRAFTMASTER RX Coronary Stent Graft is constructed using a sandwich technique, whereby an ultra-thin layer of expandable polytetrafluoroethylene (PTFE) is placed between two GRAFTMASTER stents, which are then pre-mounted on a balloon catheter delivery system. The stents are fabricated from medical-grade 316L stainless steel.

The GRAFTMASTER RX delivery system is a rapid exchange co-axial design with the balloon and stent graft at the distal end of the catheter. The proximal lumen provides for inflation of the balloon with contrast medium. The central distal lumen permits a guide wire to be inserted through the lumen. The annular space between the distal outer member and the central distal lumen provides a fluid passage path from the proximal lumen to the balloon. The shaft of the catheter, the tip, and the tapers of the balloon are coated with HYDROCOAT® hydrophilic coating.

Two radiopaque markers located on the distal end of the inner member are positioned to mark the working length of the balloon. The radiopaque markers fluoroscopically aid in positioning the stent graft pre-deployment and the delivery system for post-deployment dilatation. The balloon is designed to deliver an expandable stent graft of known diameter and length at specified pressures. Markers located on the proximal outer shaft help the physician gauge the delivery catheter position relative to the guiding catheter tip.

An adaption arm on the proximal end of the catheter provides access to the inflation lumen. It is designed with a luer-lock fitting to facilitate connection to an inflation device.

**Note:** During stent graft deployment with the stent graft delivery system from crimped state to 4.8 mm, the stent graft may shorten up to 20%. Maximum post dilatation that can be achieved with a noncompliant post dilatation balloon is a maximum of 5.5 mm. With expansion to this diameter, the system may shorten up to 25%. When choosing a GRAFTMASTER RX system for expansion in larger vessels, a longer stent graft length is recommended to ensure the treatment area is covered by the stent graft.

2.0 HOW SUPPLIED
**Sterile** – This device is sterilized with ethylene oxide gas. Non-pyrogenic. It is intended for **single use only. Do not resterilize.** Do not use if package is opened or damaged.

**Contents** – One (1) GRAFTMASTER RX Coronary Stent Graft System; one (1) protective sheath; one (1) Flexi-Clip; one (1) flushing tool.

**Storage** – Store in a dry, dark, cool place.

3.0 INDICATIONS
The GRAFTMASTER RX is indicated for use in the treatment of free perforations, defined as free contrast extravasation into the pericardium, in native coronary vessels or saphenous vein bypass grafts ≥ 2.75 mm in diameter. The effectiveness of this device for this use has not been demonstrated. Long-term outcome for this permanent implant is unknown at present.

4.0 CONTRAINDICATIONS
The GRAFTMASTER RX is contraindicated for use in:
- Patients in whom antiplatelet and / or anticoagulation therapy is contraindicated
- Patients who are judged to have a treatment area that prevents complete inflation of an angioplasty balloon or proper placement of the stent graft

5.0 WARNINGS
Ensure that the sterile barrier has not been opened or damaged prior to use.

Judicious selection of patients is necessary, since the use of this device carries the associated risk of subacute thrombosis, vascular complications, and / or bleeding events.

Persons allergic to 316L stainless steel (including the major elements iron, chromium, nickel, molybdenum) or PTFE may suffer an allergic reaction to this implant.

When multiple stents are required, stent materials should be of similar composition. Placing multiple stents of different metals in contact with each other may increase the potential for corrosion. The risk of *in vivo* corrosion does not appear to increase based on *in vitro* corrosion tests using an L-605 CoCr alloy stent (MULTI-LINK VISION® Coronary Stent) in combination with a 316L stainless steel alloy stent (MULTI-LINK TETRA Coronary Stent).
6.0 PRECAUTIONS

6.1 General Precautions
Implantation of the stent graft should be performed only by physicians who have received appropriate training.

Subsequent restenosis may require repeat dilatation of the arterial segment containing the stent graft. The long-term outcome following repeat dilatation of endothelialized stent grafts is unknown at present.

Care should be taken to control the guiding catheter tip during stent graft delivery, deployment, and balloon withdrawal. Before withdrawing the stent graft delivery system, visually confirm complete balloon deflation by fluoroscopy to avoid guiding catheter movement into the vessel and subsequent arterial damage.

Carefully read all instructions prior to use. Observe all warnings and precautions noted throughout these instructions. Failure to do so may result in complications.

Note the product “Use by” date specified on the package.

6.2 Stent Graft Handling – Precautions
This device is intended for single-use only; do not reuse. Do not resterilize, as this can compromise the device performance and increase the risk of cross contamination due to inappropriate reprocessing.

Do not remove the stent graft from its delivery system.
Removing the stent graft from the delivery system may damage the stent graft and / or lead to stent graft embolization.

The delivery system should not be used in conjunction with other stents.

Special care must be taken not to handle or in any way disrupt the stent graft position on the delivery system. This is most important during placement over the guide wire and the advancement through the hemostasis valve adaptor and guiding catheter hub.

Excessive manipulation (e.g., rolling the mounted stent graft) may cause dislodgement of the stent graft from the delivery balloon.

Do not manipulate, touch, or handle the stent graft with your fingers, as this may cause contamination or dislodgement of the stent graft from the delivery balloon.

Use only the appropriate balloon inflation media. Do not use air or any gaseous medium to inflate the balloon, as it may cause uneven expansion and difficulty in deployment of the stent graft.

6.3 Stent Graft Placement – Precautions

6.3.1 Stent Graft Preparation – Precautions
Do not prepare or pre-inflate balloon prior to stent graft deployment other than as directed. Use the balloon purging technique described in Section 10.2.3 Delivery System Preparation.

While introducing the delivery system into the vessel, do not induce negative pressure on the delivery system. This may cause dislodgement of the stent graft from the balloon.

Use guiding catheters which have lumen sizes that are suitable to accommodate the stent graft delivery system (See Section 10.1 Materials Required or product label).

6.3.2 Stent Graft Implantation – Precautions
Pre-dilatations of the vessel must take into account proximal atherosclerotic plaque beyond the treatment area, which may prevent advancement of the device to the treatment area. Failure to do so may increase the difficulty of stent graft placement and cause procedural complications.

Implanting a stent graft may lead to dissection of the vessel distal and / or proximal to the stent graft, and may cause closure of the vessel, requiring additional intervention (e.g., coronary artery bypass surgery, further dilatation, placement of additional stents, etc.).

If more than one stent graft is required, the distal stent graft should be placed initially, followed by placement of the proximal stent graft. Stent graft placement in this order obviates the need to cross the proximal stent graft when placing the distal stent graft, and reduces the chances for dislodging the proximal stent graft.

Do not expand the stent graft if it is not properly positioned in the vessel. (See Section 6.4 Stent Graft / System Removal – Precautions.)

Placement of a stent graft has the potential to compromise side-branch patency.

Do not exceed the rated burst pressure (RBP) as indicated on the product label. Monitor balloon pressures during inflation. Use of pressures higher than specified on the product label may result in a ruptured balloon with possible intimal damage and dissection.

An unexpanded stent graft may be retracted into the guiding catheter one time only. An unexpanded stent graft should not be reintroduced into the artery once it has been pulled back into the guiding catheter. Subsequent movement in and out through the distal end of the guiding catheter could cause irreparable damage to the stent graft and the delivery system.
catheter should not be performed, as the stent graft may be damaged when retracting the undeployed stent graft back into the guiding catheter. Stent graft retrieval methods (use of additional wires, snares, and / or forceps) may result in additional trauma to the vasculature and / or the vascular access site. Complications may include bleeding, hematoma, or pseudoaneurysm.

6.4 Stent Graft / System Removal – Precautions

6.4.1 Removal of the Delivery System Prior to Stent Graft Deployment

If removal of the stent graft system is required prior to deployment, ensure that the guiding catheter is coaxially positioned relative to the stent graft delivery system, and cautiously withdraw the stent graft delivery system into the guiding catheter.

Should unusual resistance be felt at any time, either during access of the treatment area or during removal of the delivery system post-stent graft implantation, the delivery system and guiding catheter should be removed as a single unit. This must be done under direct visualization and fluoroscopy.

6.4.2 Withdrawal of the Stent Graft Delivery System from the Deployed Stent Graft

1. Deflate the balloon by pulling negative on the inflation device. Confirm balloon deflation under fluoroscopy and wait 10 – 15 seconds longer.
2. Position the inflation device to “negative” or “neutral” pressure.
4. Gently remove the stent graft delivery system with slow and steady pressure.
5. Tighten the rotating hemostatic valve.

Note: If, during withdrawal of the catheter, resistance is encountered, use the following steps to improve balloon rewrap:

- Re-inflate the balloon up to nominal pressure.
- Repeat steps 1 through 5 above.

Failure to follow these steps and / or applying excessive force to the delivery system can potentially result in loss or damage to the stent graft and / or delivery system components.

If it is necessary to retain guide wire position for subsequent artery / treatment area access, leave the guide wire in place and remove all other system components. Retrieval methods (i.e., additional wires, snares, and / or forceps) may result in additional trauma to the coronary vasculature and / or the vascular access site. Complications may include, but are not limited to, bleeding, hematoma, or pseudoaneurysm.

6.5 Post-Stent Graft Placement – Precautions

Care must be exercised when crossing a newly deployed stent graft with an intravascular ultrasound (IVUS) catheter, a coronary guide wire, a balloon catheter, or delivery system to avoid disrupting the stent graft geometry, apposition, and / or geometry.

Antiplatelet therapy should be administered post-procedure (See Section 9.0 Individualization of Treatment). Patients who require early discontinuation of antiplatelet therapy (e.g., secondary to active bleeding) should be monitored carefully for cardiac events. At the discretion of the patient’s treating physician, the antiplatelet therapy should be restarted as soon as possible.

If the patient requires imaging, see Section 6.6 MRI Statement.

6.6 MRI Statement

Nonclinical testing has demonstrated that the GRAFTMASTER RX Coronary Stent Graft, in single and in overlapped configurations up to 44 mm in length, is MR Conditional. It can be scanned safely under the following conditions:

- Static magnetic field of 1.5 or 3 Tesla
- Spatial gradient field of 2500 Gauss/cm or less
- Maximum whole-body-averaged specific absorption rate (SAR) of 2.0 W/kg (normal operating mode) for up to 15 minutes of scanning for each duration of a sequence

The GRAFTMASTER stent graft should not migrate in this MRI environment. Nonclinical testing at field strengths greater than 3 Tesla has not been performed to evaluate stent graft migration or heating. MRI at 1.5 or 3 Tesla may be performed immediately following the implantation of the GRAFTMASTER stent graft.

Stent graft heating was derived by using the measured nonclinical, in vitro temperature rises in a GE Excite 3 Tesla scanner and in a GE 1.5 Tesla coil in combination with the local specific absorption rates (SARs) in a digitized human
The maximum whole-body-averaged SAR was determined by validated calculation. At overlapped lengths of up to 44 mm, the GRAFTMASTER stent graft produced a nonclinical maximum local temperature rise of 1.8°C at a maximum whole-body-averaged SAR of 2.0 W/kg (normal operating mode) for 15 minutes. These calculations do not take into consideration the cooling effects of blood flow.

The effects of MRI on overlapped stent grafts greater than 44 mm in length or stent grafts with fractured struts are unknown.

As demonstrated in nonclinical testing, the image artifact extends approximately 15 mm from the device, both inside and outside the device lumen, when scanned using the sequence: gradient echo in a 3T GE Sigma HDxt software release 15.0_M4_0910.z MR system with a Body Transmit coil. Therefore, it may be necessary to optimize the MR imaging parameters for the presence of the GRAFTMASTER stent graft.

It is suggested that patients register the conditions under which the implant can be safely scanned with the MedicAlert Foundation (www.medicalert.org) or an equivalent organization.

7.0 ADVERSE EVENTS

Data were collected from a total of 41 patients in a multicenter, retrospective analysis of use of the physician-mounted JOSTENT® Coronary Stent Graft to treat perforations. These patients form the basis of the observed adverse events reported. (See Section 8.0 Clinical Study.)

7.1 Observed Adverse Events

A total of 14 of 41 patients (34.1%) receiving the JOSTENT Coronary Stent Graft experienced one or more adverse events during the procedure. Only one patient (1/41, 2.4%) experienced events post-JOSTENT implantation, due to an incompletely sealed perforation. All other adverse events can be attributed to the perforation since they occurred prior to stent graft implantation.

No patients who received the JOSTENT Coronary Stent Graft died, experienced a Q-wave myocardial infarction (MI), or necessitated emergent CABG during the procedure or in-hospital stay. All stent grafts were successfully delivered.

### Table 1: Procedural Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>N occurrences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Adverse Event</td>
<td>14 (35.0%)</td>
</tr>
<tr>
<td>Procedural Complications</td>
<td></td>
</tr>
<tr>
<td>Pericardial effusion</td>
<td>9 (22.5%)</td>
</tr>
<tr>
<td>Tamponade</td>
<td>5 (12.5%)</td>
</tr>
<tr>
<td>Pericardiocentesis</td>
<td>6 (15.0%)</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>1 (2.5%)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>5 (12.5%)</td>
</tr>
<tr>
<td>Cardiogenic shock</td>
<td>4 (10.0%)</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>4 (10.0%)</td>
</tr>
</tbody>
</table>

1 All complications occurred in the cardiac catheterization laboratory prior to JOSTENT Stent Graft implantation, except for a single out-of-lab effusion that progressed to tamponade and required emergent re-PTCA (percutaneous transluminal coronary angioplasty) with placement of a second JOSTENT Stent Graft, which sealed the perforation.

### Table 2: In-hospital Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>N occurrences</th>
<th>Historical Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>0</td>
<td>Free Perforations: 20%</td>
</tr>
<tr>
<td>Emergent CABG</td>
<td>0</td>
<td>60%</td>
</tr>
<tr>
<td>Q-wave MI</td>
<td>0</td>
<td>10%</td>
</tr>
</tbody>
</table>

7.2 Potential Adverse Events

Adverse events (in alphabetical order) that may be associated with the use of the GRAFTMASTER RX Coronary Stent Graft in native coronary arteries may include:

- Acute myocardial infarction
- Arrhythmias (including ventricular fibrillation and ventricular tachycardia)
- Coronary artery bypass surgery
- Death
- Dissection
- Drug reactions to antiplatelet agents / contrast medium
- Emboli, distal (air, tissue, or thrombotic emboli)
- Emergent coronary artery bypass surgery
- Hemorrhage, requiring transfusion
- Hypotension / hypertension
- Infection and pain at insertion site
- Ischemia, myocardial
- Perforation
- Pseudoaneurysm, femoral
- Restenosis of stented segment
- Spasm
- Stent graft embolization
- Stent graft thrombosis / occlusion
- Stroke / cerebrovascular accidents
- Total occlusion of coronary artery

8.0 CLINICAL STUDY

8.1 Objective

The objective of this study was to evaluate the technical success and safety of the JOSTENT Coronary Stent Graft as a life-saving treatment in cases of coronary artery perforation.

8.2 Design

This study was multicenter, retrospective, and nonrandomized. Demographic, clinical, and angiographic data were collected on the target population, including in-hospital and limited follow-up data.

Abbott Vascular Devices is aware of a total of 46 perforations treated worldwide with the physician-mounted JOSTENT Coronary Stent Graft. Full procedural case report forms have been received for 41 of the 46 subjects. Follow-up forms were received for 27 of the 41 evaluable subjects.

The follow-up time ranged from one week to one year. All subjects were enrolled after undergoing urgent or emergent use of the JOSTENT Coronary Stent Graft to treat a native coronary artery or saphenous vein graft perforation.

8.3 Results

Demographics were collected for the 41 subjects. Sixty-five percent of the subjects were male. The subjects had a high incidence of previous MI (59%), previous CABG (27.5%), previous PTCA (30.8%), and Canadian Cardiovascular Society Class III / IV angina (83.3%). For this population, the in-hospital major adverse cardiac event (MACE) rate was 0%. There were no in-hospital incidents of death, Q-wave MI, or emergent CABG. In all cases, the JOSTENT Coronary Stent Graft was deployed successfully. No device malfunctions were noted. In all cases, the perforation was sealed.

<table>
<thead>
<tr>
<th>Table 3: Summary Table</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>JOSTENT deployed successfully</td>
</tr>
<tr>
<td>Perforation closed / vessel sealed</td>
</tr>
<tr>
<td>In-hospital MACE</td>
</tr>
<tr>
<td>Death</td>
</tr>
<tr>
<td>Emergent CABG</td>
</tr>
<tr>
<td>Q-wave MI</td>
</tr>
</tbody>
</table>
### Table 4: Patient Demographics

<table>
<thead>
<tr>
<th></th>
<th>Occurrences (%)</th>
<th>Not reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average age, years</td>
<td>65.2</td>
<td>1</td>
</tr>
<tr>
<td>Male</td>
<td>26 (65.0%)</td>
<td>1</td>
</tr>
<tr>
<td>Hx of MI</td>
<td>23 (59.0%)</td>
<td>2</td>
</tr>
<tr>
<td>Hx of CAD</td>
<td>30 (75%)</td>
<td>1</td>
</tr>
<tr>
<td>Hx of CABG</td>
<td>11 (27.5%)</td>
<td>1</td>
</tr>
<tr>
<td>Hx of PTCA</td>
<td>12 (30.8%)</td>
<td>2</td>
</tr>
<tr>
<td>Hx of CHF</td>
<td>2 (6.4%)</td>
<td>10</td>
</tr>
<tr>
<td>Hx of HTN</td>
<td>11 (36.7%)</td>
<td>11</td>
</tr>
<tr>
<td>Angina</td>
<td>41 (100%)</td>
<td>–</td>
</tr>
<tr>
<td>Class I / II</td>
<td>6 (16.7%)</td>
<td>5</td>
</tr>
<tr>
<td>Class III / IV</td>
<td>30 (83.3%)</td>
<td>5</td>
</tr>
<tr>
<td>Diabetes</td>
<td>6 (23.1%)</td>
<td>15</td>
</tr>
</tbody>
</table>

1 Procedural forms were never received for 5 of the total 46 cases reported to Abbott Vascular Devices. No information has been received regarding these cases.

### Table 5: Procedural Information

<table>
<thead>
<tr>
<th></th>
<th>N occurrences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Index procedure elective</td>
<td>38/40 (95.0%)</td>
</tr>
<tr>
<td>Index procedure emergent</td>
<td>2/40 (5.0%)</td>
</tr>
<tr>
<td>JOSTENT indication</td>
<td></td>
</tr>
<tr>
<td>Perforation</td>
<td>37 (90.2%)</td>
</tr>
<tr>
<td>Others: Aneurysm</td>
<td>1</td>
</tr>
<tr>
<td>Fistula</td>
<td>2</td>
</tr>
<tr>
<td>Rescue after embolized stent graft</td>
<td>1</td>
</tr>
<tr>
<td>Native vessel</td>
<td>33 (80.5%)</td>
</tr>
<tr>
<td>SVG</td>
<td>8 (19.5%)</td>
</tr>
<tr>
<td>Average number of stent grafts used</td>
<td>1.3 (range: 1 – 3)</td>
</tr>
<tr>
<td>JOSTENT Stent Graft deployed successfully</td>
<td>52 (100%)</td>
</tr>
<tr>
<td>Perforation closed / vessel sealed</td>
<td>41 (100%)</td>
</tr>
</tbody>
</table>

### Table 6: In-hospital MACE

<table>
<thead>
<tr>
<th></th>
<th>N occurrences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>0</td>
</tr>
<tr>
<td>Emergent CABG</td>
<td>0</td>
</tr>
<tr>
<td>Q-wave MI</td>
<td>0</td>
</tr>
</tbody>
</table>

### Table 7: Procedural Complications

<table>
<thead>
<tr>
<th></th>
<th>N occurrences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients experience any complication</td>
<td>14 (34.1%)</td>
</tr>
<tr>
<td>Procedural Complications¹</td>
<td></td>
</tr>
<tr>
<td>Pericardial effusion</td>
<td>9 (22.0%)</td>
</tr>
<tr>
<td>Tamponade</td>
<td>5 (12.2%)</td>
</tr>
<tr>
<td>Pericardiocentesis</td>
<td>6 (14.6%)</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>1 (2.4%)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>5 (12.2%)</td>
</tr>
<tr>
<td>Cardiogenic shock</td>
<td>4 (9.8%)</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>4 (9.8%)</td>
</tr>
</tbody>
</table>

¹ All complications occurred in the cardiac catheterization laboratory prior to JOSTENT Stent Graft implantation, except for a single out-of-lab effusion that progressed to tamponade and required emergent re-PTCA with placement of a second JOSTENT Stent Graft that sealed the perforation.

### Table 8: Complications at Follow-up

<table>
<thead>
<tr>
<th></th>
<th>N occurrences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target vessel / lesion revascularization (TVR / TLR)</td>
<td>4</td>
</tr>
<tr>
<td>TVR only</td>
<td>1</td>
</tr>
<tr>
<td>Myocardial Infarction (MI)</td>
<td>3</td>
</tr>
<tr>
<td>Non-Q-wave MI</td>
<td>2</td>
</tr>
<tr>
<td>Occlusion of the target lesion¹</td>
<td>2</td>
</tr>
<tr>
<td>Revascularization¹</td>
<td>1</td>
</tr>
</tbody>
</table>

¹ No further information was provided.
8.4 Conclusions
The clinical data from a small, retrospective study suggest that the physician-mounted JOSTENT Coronary Stent Graft can be deployed in coronary arteries to seal free perforations. These data also suggest that the use of the JOSTENT Coronary Stent Graft is not associated with increased risks compared to conventional treatment of perforations.

9.0 INDIVIDUALIZATION OF TREATMENT
The risks and benefits described above should be carefully considered for each patient before use of the GRAFTMASTER RX Coronary Stent Graft System. Patient selection factors to be assessed should include a judgment regarding risk of prolonged anticoagulation. Stent graft placement is generally avoided in those patients at heightened risk of bleeding (e.g., those patients with recently active gastritis or peptic ulcer disease).

9.1 Use in Special Populations
The effectiveness of this device for any use has not been demonstrated. The safety of the GRAFTMASTER RX Coronary Stent Graft System has not been established for patients with any of the following characteristics:

- Patients with unresolved vessel thrombus at the treatment area
- Patients with coronary artery reference vessel diameters < 2.75 mm
- Patients with treatment areas located in the unprotected left main coronary artery, ostial treatment areas, or treatment areas located at a bifurcation
- Patients with diffuse disease or poor outflow distal to the identified treatment areas
- Patients with recent acute myocardial infarction, where there is evidence of thrombus or poor flow
- Patients with more than two overlapping stents due to risk of thrombus or poor flow

The safety and effectiveness of using mechanical atherectomy devices (directional atherectomy catheters, rotational atherectomy catheters) or laser angioplasty catheters to treat in-stent stenosis have not been established.

10.0 OPERATOR’S MANUAL

10.1 Materials Required
- Appropriate guiding catheter(s) – 7F / 0.074” ID for 4.50 – 4.80 mm diameter GRAFTMASTER RX, or 6F / 0.068” ID for 2.80 mm – 4.00 mm diameter GRAFTMASTER RX
- 2 – 3 syringes (10 – 20 cc)
- 1,000 u/500 cc heparinized normal saline (HepNS)
- 0.014 inch (0.36 mm) x 175 cm (minimum length) guide wire
- Rotating hemostatic valve with 0.096 inch (2.44 mm) minimum inner diameter
- Contrast material diluted 1:1 with normal saline
- Inflation device
- Three-way stopcock
- Torque device
- Guide wire introducer
- Appropriate arterial sheath
- Appropriate anticoagulation and antiplatelet drugs

10.2 System Preparation
Note: During stent graft deployment with the stent delivery system from crimped state to 4.8 mm, the graft may shorten up to 20%.

10.2.1 Packaging Removal
Carefully remove the delivery system from its protective tubing for preparation of the delivery system. Do not bend or kink the hypotube during removal.

Remove the product mandrel and protective stent graft sheath by grasping the catheter just proximal to the stent graft (at the proximal balloon bond site), and with the other hand, grasp the stent graft protector and gently remove distally. If unusual resistance is felt during product mandrel and stent graft sheath removal, do not use this product and replace with another. Follow product returns procedure for the unused device.

Visually inspect the stent graft for uniformity, protruding coils, and centering on the balloon and verify that the stent graft does not extend beyond the radiopaque balloon markers.

10.2.2 Guide Wire Lumen Flush
Flush the guide wire lumen with HepNS using the flushing tool supplied with the product. Insert the flushing tool into the tip of the catheter and flush until fluid exits the guide wire exit notch.
Note: Avoid manipulation of the stent graft while flushing the guide wire lumen, as this may disrupt the placement of the stent graft on the balloon.

10.2.3 Delivery System Preparation
1. Prepare an inflation device / syringe with diluted contrast medium.
2. Attach an inflation device / syringe to the stopcock and attach it to the inflation port of the product. Do not bend the product hypotube when connecting to the inflation device / syringe.
3. With the tip down, orient the delivery system vertically.
4. Open the stopcock to the delivery system, pull negative for 30 seconds, and release to neutral for contrast fill.
5. Close the stopcock to the delivery system and purge the inflation device / syringe of all air.
6. Repeat steps 3 through 5 until all air is expelled. If bubbles persist, do not use the product.
7. If a syringe was used, attach a prepared inflation device to the stopcock.
8. Open the stopcock to the delivery system.
9. Leave on neutral.
10. Moisten the stent graft with heparinized saline by submerging the stent graft into a sterile bowl containing the solution. Note: Do not use gauze sponges to wipe down the stent graft as fibers may disrupt the stent graft.

Note: While introducing the delivery system into the vessel, do not induce negative pressure on the delivery system. This may cause dislodgement of the stent graft from the balloon.

Note: If air is seen in the shaft, repeat steps 3 through 5 to prevent uneven stent graft expansion.

10.3 Delivery Procedure
1. Prepare the vascular access site according to standard practice.
2. Pre-dilatations of the vessel must take into account proximal atherosclerotic plaque beyond the treatment area, which may prevent advancement of the device to the treatment area. Failure to do so may increase the difficulty of the stent graft placement and cause procedural complications.
3. Maintain neutral pressure on the inflation device attached to the delivery system. Open the rotating hemostatic valve as widely as possible.
4. Backload the delivery system onto the proximal portion of the guide wire while maintaining guide wire position across the treatment area.
5. Carefully advance the delivery system into the guiding catheter and over the guide wire to the treatment area. Be sure to keep the hypotube straight. Ensure guiding catheter stability before advancing the stent graft system into the coronary artery.
6. Advance the delivery system over the guide wire to the treatment area under direct fluoroscopic visualization. Utilize the radiopaque balloon markers to position the stent graft across the treatment area. Perform angiography to confirm stent graft position. If the position of the stent graft is not optimal, it should be carefully repositioned or removed. Expansion of the stent graft should not be undertaken if the stent graft is not properly positioned in the treatment area.

CAUTION: If resistance is encountered, do not force passage. Resistance may indicate damage to the device or movement of the stent graft on the balloon.

Note: If removal of a stent graft system is required prior to deployment, ensure that the guiding catheter is coaxially positioned relative to the stent graft delivery system, and cautiously withdraw the stent graft delivery system into the guiding catheter. The stent graft delivery system and the guiding catheter should be removed as a single unit. This should be done under direct visualization with fluoroscopy.

7. Tighten the rotating hemostatic valve. The stent graft is now ready to be deployed.

CAUTION: Avoid over-tightening the Tuohy-Borst valve, as this may restrict the flow of contrast medium in and out of the balloon, thereby slowing inflation / deflation.

10.4 Deployment Procedure
CAUTION: Refer to the product label for in vitro stent graft outer diameter, nominal pressure, and RBP.
1. Prior to deployment, reconfirm the correct position of the stent graft relative to the treatment area using the radiopaque balloon markers.
2. Deploy the stent graft slowly by pressurizing the delivery system in 2-atm increments, every 5 seconds, until the stent graft is completely expanded. Fully expand the stent graft by inflating to nominal pressure at a minimum. Accepted practice generally targets an initial deployment pressure that would achieve a stent graft
inner diameter ratio of about 1.1 times the reference vessel diameter (refer to product label for in vitro stent graft inner diameter, nominal pressure, and RBP).

3. Maintain pressure for 30 seconds. If necessary, the delivery system can be repressurized or further pressurized to ensure complete apposition of the stent graft to the artery wall. Maintain pressure for 30 seconds for full expansion of the stent graft. Fluoroscopic visualization during stent graft expansion should be used in order to properly judge the optimum stent graft diameter as compared to the proximal and distal native coronary artery diameters (reference vessel diameters). Optimal stent graft expansion and proper apposition require that the stent graft be in full contact with the arterial wall.

Note: See Section 10.5 Removal Procedure for instruction on withdrawal of stent graft delivery system.

4. If necessary, the delivery system can be repressurized or further pressurized to ensure complete apposition of the stent graft to the artery wall.

CAUTION: Do not exceed the labeled RBP of 16 atm (1621 kPa).

5. Deflate the balloon by pulling negative on the inflation device for 30 seconds. Confirm complete balloon deflation before attempting to move the delivery system. If unusual resistance is felt during stent graft delivery system withdrawal, pay particular attention to guiding catheter position.

6. Confirm stent graft position and deployment using standard angiographic techniques. Fluoroscopic visualization during stent graft expansion should be used in order to properly judge the optimum expanded stent graft diameter as compared to the proximal and distal coronary artery diameter(s). Optimal expansion requires that the stent graft be in full contact with the artery wall. Stent graft wall contact should be verified through routine angiography.

7. If the deployed stent graft size is still inadequate with respect to reference vessel diameter, a larger balloon may be used to further expand the stent graft. If the initial angiographic appearance is suboptimal, the stent graft may be further expanded using a low profile, high pressure, noncompliant balloon dilation catheter. If this is required, the stented segment should be carefully recrossed with a prolapsed guide wire to avoid disrupting the stent graft geometry. Deployed stent graft should not be left underdilated.

Note: Maximum post dilatation that can be achieved with a noncompliant post dilatation balloon is a maximum of 5.5 mm. With expansion to this diameter the system may shorten up to 25%. When choosing a GRAFTMASTER RX system for expansion in larger vessels, a longer stent graft length is recommended to ensure the treatment area is covered by the stent graft.

CAUTION: Do not dilate the stent graft beyond 5.5 mm.

10.5 Removal Procedure

Withdrawal of the Stent Graft Delivery System from the Deployed Stent Graft:

1. Deflate the balloon by pulling negative on the inflation device. Confirm balloon deflation under fluoroscopy and wait 10 – 15 seconds longer.

2. Position the inflation device to “negative” or “neutral” pressure.


4. Gently remove the stent graft delivery system with slow and steady pressure.

5. Tighten the rotating hemostatic valve.

Note: If, during withdrawal of the catheter, resistance is encountered, use the following steps to improve balloon rewrap:

- Re-inflate the balloon up to nominal pressure.
- Repeat steps 1 through 5 above.
## 11.0 IN VITRO INFORMATION

### Table 9: GRAFTMASTER RX Compliance Chart – Stent Graft Inner Diameter vs. Pressure

<table>
<thead>
<tr>
<th>Pressure</th>
<th>Stent ID (mm) by System Diameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>atm</td>
<td>kPa</td>
</tr>
<tr>
<td>11</td>
<td>1115</td>
</tr>
<tr>
<td>12</td>
<td>1216</td>
</tr>
<tr>
<td>13</td>
<td>1317</td>
</tr>
<tr>
<td>14</td>
<td>1419</td>
</tr>
<tr>
<td>15 (nominal)</td>
<td>1520</td>
</tr>
<tr>
<td>16 (RBP)*</td>
<td>1621</td>
</tr>
</tbody>
</table>

### Table 10: GRAFTMASTER RX Compliance Chart – Stent Graft Outer Diameter vs. Pressure

<table>
<thead>
<tr>
<th>Pressure</th>
<th>Stent OD (mm) by System Diameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>atm</td>
<td>kPa</td>
</tr>
<tr>
<td>11</td>
<td>1115</td>
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<tr>
<td>12</td>
<td>1216</td>
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<td>1317</td>
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<tr>
<td>14</td>
<td>1419</td>
</tr>
<tr>
<td>15 (nominal)</td>
<td>1520</td>
</tr>
<tr>
<td>16 (RBP)*</td>
<td>1621</td>
</tr>
</tbody>
</table>

**Note:** These nominal data are based on in vitro testing at 37°C and do not take into account treatment area resistance. Ensure full deployment of the stent graft (See Section 10.4 Deployment Procedure) and confirm the stent graft sizing angiographically.

*Do not exceed the RBP.

### 12.0 TRADEMARKS

GRAFTMASTER, HYDROCOAT, MULTI-LINK VISION, and JOSTENT are registered trademarks of the Abbott Group of Companies.
GRAFTMASTER
Coronary Stent Graft System

The GRAFTMASTER Coronary Stent Graft is commercially approved by the U.S. Food and Drug Administration (FDA) for use in the treatment of free coronary perforations, defined as a tear in the wall of either the coronary artery or the saphenous (leg) vein bypass graft that allows fluids from the artery or vein bypass graft to leak into the lining that encloses the heart. This is known as a perforation which can occur during a coronary vessel procedure.

The FDA has approved the GRAFTMASTER Coronary Stent Graft as a Humanitarian Use Device (HUD). A HUD is a device that is intended to benefit patients with rare diseases or conditions. There is no comparable device available to treat this condition or existing alternatives are not feasible for a specific patient. The FDA concluded from available data the probable benefits of the device outweigh the probable risks for this indication. Although FDA-approved, the effectiveness of HUDs (including the GRAFTMASTER) has not been proven. Long term outcome for this permanent implant is unknown at present.

Vessel Location
For any questions regarding your stent or procedure, please contact your implanting physician.

Aortic Arch
LM
Left Main
LAD
Left Anterior Descending
Circumflex
OM
Obtuse Marginal
Diagonal
Bypass Graft
RCA
Right Coronary Artery
PD
Posterior Descending
AM
Acute Marginal
The GRAFTMASTER stent graft consists of two high-grade surgical steel flexible stents with an expandable graft material sandwiched between the two stents.

The stent graft is delivered using a balloon and placed at the site of the perforation. The balloon is inflated thereby expanding the stent and securing it in position. The GRAFTMASTER Coronary Stent Graft closes the perforation (hole) preventing blood from escaping into the heart sac. It also allows the blood supply in your coronary artery to return to normal.

Patients who have an allergy to stainless steel may suffer an allergic reaction to this implant. If you experience any difficulty, please contact your physician immediately, or seek emergency care for any side effects you may be experiencing.

If you would like additional information about your GRAFTMASTER Coronary Stent Graft, please talk with your treating physician, or contact Abbott Vascular at 1-800-227-9902. Additionally, you will receive a GRAFTMASTER Coronary Stent Graft Patient Identification Card to carry in your wallet.

It is suggested that patients register the conditions under which the implant can safely be scanned with the MedicAlert Foundation (www.medicalert.org) or an equivalent organization.

GRAFTMASTER is a registered trademark of the Abbott Group of Companies.
Caution: This product is intended for use by or under the direction of a physician. Prior to use, it is important to read the package insert thoroughly for Instructions for Use, Warnings and Potential Complications associated with use of these devices.

All illustrations included are artist’s renditions. Not drawn to scale. GRAFTMASTER is a trademark of the Abbott Group of Companies.