Humanitarian Use Devices/Humanitarian Device Exemptions in Cardiovascular Medicine

Aaron V. Kaplan, MD; Elisa D. Harvey, DVM, PhD; Richard E. Kuntz, MD; Hadas Shiran, BS; John F. Robb, MD; Peter Fitzgerald, MD, PhD

Abstract—The Second Dartmouth Device Development Symposium held in October 2004 brought together leaders from the medical device community, including clinical investigators, senior representatives from the US Food and Drug Administration, large and small device manufacturers, and representatives from the financial community to examine difficult issues confronting device development. The role of the Humanitarian Use Device/Humanitarian Device Exemption (HUD/HDE) pathway in the development of new cardiovascular devices was discussed in this forum. The HUD/HDE pathway was created by Congress to facilitate the availability of medical devices for “orphan” indications, ie, those affecting <4000 individuals within the United States each year. The HUD/HDE pathway streamlines the approval process and permits less well-characterized devices to enter the market. HDE approval focuses primarily on issues of safety and scientific soundness and does not require demonstration of efficacy. In the 7 years since the first device was approved in 1997, a total of 35 HDEs have been granted (23 devices, 6 diagnostic tests). As the costs to gain regulatory approval for commonly used devices increase, companies often seek alternative ways to gain market access, including the HUD/HDE pathway. For a given device, there may be multiple legitimate and distinct indications, including indications that meet the HUD criteria. Companies must choose how and when to pursue each of these indications. The consensus of symposium participants was for the HUD/HDE pathway to be reserved for true orphan indications and not be viewed strategically as part of the clinical development plan to access a large market. (Circulation. 2005;112:2883-2886.)

Key Words: heart disease ■ catheterization ■ surgery ■ catheter
TABLE 1. HUD/HDE Approved Devices

<table>
<thead>
<tr>
<th>Device Description</th>
<th>Year</th>
<th>Company/Sponsor</th>
<th>Implant</th>
<th>Ped</th>
<th>Vasc</th>
<th>Ortho</th>
<th>Uro</th>
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<tbody>
<tr>
<td>Vertical Expandable Prosthetic Titanium Rib</td>
<td>2004</td>
<td>Synthes, Inc</td>
<td>1</td>
<td>1</td>
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<tr>
<td>OP-1 Putty</td>
<td>Bioabsorbent</td>
<td>2004</td>
<td>Stryker, Corp</td>
<td>1</td>
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<td></td>
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<tr>
<td>DeBailey-Child Left Ventricular Assist System</td>
<td>Pediatric LVAD</td>
<td>2004</td>
<td>MicroMed Technology, Inc</td>
<td>1</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Heartbreath Cardiac Cardioplegia</td>
<td>Cardiac rejection assay</td>
<td>2004</td>
<td>Meninas Research, Inc</td>
<td>1</td>
<td></td>
<td></td>
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<tr>
<td>CONTEGRA Pulmonary Valved Conduit</td>
<td>Pulmonic valve</td>
<td>2003</td>
<td>Medtronic, Inc</td>
<td>1</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Dermalgraft</td>
<td>Artificial skin</td>
<td>2003</td>
<td>Smith/Nephew, Inc</td>
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<td></td>
<td></td>
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<tr>
<td>Activa Dystonia Therapy</td>
<td>Neurostimulation</td>
<td>2003</td>
<td>Medtronic, Inc</td>
<td>1</td>
<td>1</td>
<td>1</td>
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<td>Astromark Microdevice Stent System</td>
<td>Neuroradiologic stent</td>
<td>2002</td>
<td>Smart Therapeutics, Inc</td>
<td>1</td>
<td>1</td>
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<tr>
<td>NEURLINK Stent &amp; Delivery Catheter</td>
<td>Neuroradiologic stent</td>
<td>2002</td>
<td>Guidant Corp</td>
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<td>Amplatz PFO Occluder</td>
<td>PFO occluder</td>
<td>2002</td>
<td>AGA Medical Corp</td>
<td>1</td>
<td>1</td>
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<td>Ascension PIP</td>
<td>Orthopedic implant–joint</td>
<td>2002</td>
<td>Ascension Orthopedics</td>
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<td>VISX Custom Contoured Ablation Pattern</td>
<td>Ophthalmologic laser pattern</td>
<td>2001</td>
<td>VISX, Inc</td>
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<tr>
<td>OP-1 Implant</td>
<td>Bioabsorbent</td>
<td>2001</td>
<td>Stryker Corp</td>
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<tr>
<td>Metacarpophalangeal (MCP) Joint Implant</td>
<td>Orthopedic implant–joint</td>
<td>2001</td>
<td>Arwenta Orthopedics, Inc</td>
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<tr>
<td>PROSTALAC Hip Temporary Prosthesis</td>
<td>Orthopedic implant–hip</td>
<td>2001</td>
<td>DePuy/Johnson &amp; Johnsen</td>
<td>1</td>
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<td>Composite Culture Skin (CCS)</td>
<td>Artificial skin</td>
<td>2001</td>
<td>Ortec International, Inc</td>
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<td>JOMED JOSTENT Coronary Stent Graft</td>
<td>Coronary stent graft</td>
<td>2001</td>
<td>JOMED AB</td>
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<td>TAS Ecarin Clotting Time Test</td>
<td>Coagulation assay</td>
<td>2000</td>
<td>Cardiovascular Diagnostics, Inc</td>
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<td>Entera Therapy System</td>
<td>Gastric electrical stimulation</td>
<td>2000</td>
<td>Medtronic, Inc</td>
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<tr>
<td>Telescopic Plate Spacer (TPS) Spinal System</td>
<td>Orthopedic implant–disk</td>
<td>2000</td>
<td>InterporeCross Internat</td>
<td>1</td>
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<tr>
<td>CardioSEAL Septal Occlusion System</td>
<td>Septal occluder</td>
<td>2000</td>
<td>NMT Medical, Inc</td>
<td>1</td>
<td>1</td>
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<tr>
<td>TheraSphere MDS</td>
<td>Brachy Tx implant–hepatic Ca</td>
<td>1999</td>
<td>Nordan, Inc</td>
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<tr>
<td>BioGlue Surgical Adhesive</td>
<td>Bioabsorbent</td>
<td>1999</td>
<td>CryoLife, Inc</td>
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<tr>
<td>Shielhigh Pulmonic Valve Conduit</td>
<td>Pulmonic valve</td>
<td>1999</td>
<td>Shielhigh, Inc</td>
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<td>1</td>
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<tr>
<td>CardioSEAL Septal Occlusion System</td>
<td>Septal occluder</td>
<td>1999</td>
<td>NMT Medical, Inc</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Action Neoplastic</td>
<td>Artificial rectal sphincter</td>
<td>1999</td>
<td>American Med Systems, Inc</td>
<td>1</td>
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<tr>
<td>CardioSEAL Septal Occlusion System</td>
<td>Septal occluder</td>
<td>1999</td>
<td>NMT Medical, Inc</td>
<td>1</td>
<td>1</td>
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<tr>
<td>VOGARE Bladder System</td>
<td>Neurastimulation–bowel</td>
<td>1999</td>
<td>NeuroControl Corp</td>
<td>1</td>
<td>1</td>
<td></td>
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<tr>
<td>VOGARE Bladder System</td>
<td>Neurastimulation–bladder</td>
<td>1998</td>
<td>NeuroControl Corp</td>
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<tr>
<td>Avanta Proximal Interphalangeal Finger Prosthesis</td>
<td>Orthopedic implant–joint</td>
<td>1998</td>
<td>Avanta Orthopedics, Inc</td>
<td>1</td>
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<td></td>
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<tr>
<td>Perma-Flow Coronary Graft, Model 2C10</td>
<td>Prosthetic conduit for CABG</td>
<td>1998</td>
<td>Possis Medical, Inc</td>
<td>1</td>
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<tr>
<td>Excorin Immunoadsorption System</td>
<td>Coagulopathy treatment</td>
<td>1998</td>
<td>Cubic BCT</td>
<td>1</td>
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<td>Urethra</td>
<td>Neurastimulation–bladder control</td>
<td>1997</td>
<td>WE Kaplan &amp; I Richards</td>
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<tr>
<td>King's College Fetal Bladder Drainage Catheter</td>
<td>Fetal urologic obstruction</td>
<td>1997</td>
<td>Rocket Medical PLC</td>
<td>1</td>
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<td></td>
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</tr>
<tr>
<td>Harrison Fetal Bladder Stent Set</td>
<td>Fetal urologic obstruction</td>
<td>1997</td>
<td>Cook OB/GYN, Inc</td>
<td>1</td>
<td>1</td>
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</table>

Ped indicates pediatric; Vasc, vascular; Ortho, orthopedic; Uro, urologic; LVAD, left ventricular assist device; and PFO, patent foramen ovale.

Approval to market an HUD is a 2-part process, starting with obtaining an HUD designation, followed by HDE approval. The HUD designation is granted by the FDA’s Office of Orphan Products. The HDE designation is granted for devices designed to treat or diagnose rare conditions when no other comparable devices are available. A rare condition, for the purposes of HUD designation, is defined as a disease or condition affecting <4000 individuals within the United States each year. If the HUD designation is granted, the sponsor can then seek device approval in the form of an HDE application. The HDE application has format and approval criteria similar to an Investigational Device Exemption (IDE) application. An application for an IDE provides safety data and a rationale to support a specific clinical development plan and study design, including methodology to follow up patients both during and after the procedure. Criteria for IDE approval focus primarily on issues of safety and scientific soundness. Similarly, for HDE approval, the sponsor needs to provide a detailed description of the device, along with appropriate preclinical testing and clinical data (although not required) demonstrating device safety. Manufacturing data qualifying the device for clinical use, eg, destruction testing and sterile validation is provided to document that a comparable device is not available for the proposed indication. The Office of Orphan Products has 45 days to review the request, at which time it can approve, disapprove, or request additional information. If the HUD designation is granted, the sponsor can then seek device approval in the form of an HDE application. The HDE application has format and approval criteria similar to an Investigational Device Exemption (IDE) application. An application for an IDE provides safety data and a rationale to support a specific clinical development plan and study design, including methodology to follow up patients both during and after the procedure. Criteria for IDE approval focus primarily on issues of safety and scientific soundness. Similarly, for HDE approval, the sponsor needs to provide a detailed description of the device, along with appropriate preclinical testing and clinical data (although not required) demonstrating device safety. Manufacturing data qualifying the device for clinical use, eg, destruction testing and sterile validation is provided to document that a comparable device is not available for the proposed indication.
TABLE 2. PMA Versus HDE

<table>
<thead>
<tr>
<th></th>
<th>HDE</th>
<th>PMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Rare (&lt;4000 patients/y)</td>
<td>General</td>
</tr>
<tr>
<td>Clinical study design</td>
<td>Clinical data not absolutely required</td>
<td>Frequently RCT</td>
</tr>
<tr>
<td>IRB approval after market</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Selling price</td>
<td>Limited to Recovery Cost</td>
<td>As per market</td>
</tr>
<tr>
<td>Review time frame, d</td>
<td>75</td>
<td>180</td>
</tr>
</tbody>
</table>

RCT indicates randomized controlled trial.

As the costs to obtain device approval continue to rise, companies (especially start-up companies devoted to developing a single device) are under extreme pressure to quickly obtain evidence of the clinical benefit of a device and its market acceptance and to generate revenues. The HUD/HDE pathway provides a way for a product to quickly enter the marketplace, allowing the company to obtain early performance data and realize revenue from device sales. For a given device, there may be multiple legitimate and distinct indications, including indications that meet the HUD criteria. Companies must choose how and when to pursue each of these indications. When contemplating the strategic use of the 1997, a total of 35 HDEs have been granted for 23 devices and 6 diagnostic tests. Three devices (CardioSEAL, Septal Occlusion System, NMT Medical; the VOCARE Bladder System, NeuroControl Corp; and OP-1 Putty, Stryker Bio-tech) have received HDE approvals for multiple indications. Nearly half the HDEs granted were for vascular devices; the remaining approvals were evenly split between orthopedic and urologic indications. Approximately one quarter of the approved HUDs are for a pediatric indication. It is also interesting to note the diversity among HDE sponsors, ranging from individual caregivers (W.E. Kaplan, MD, and I. Richards, RN, MSN) to the largest device firms (Johnson & Johnson and Medtronic, Inc).7

There are important differences in the rules and regulations associated with the HUD/HDE pathway compared with the PMA pathway for general-use devices. These differences emanate from the different effectiveness standards for HDE compared with PMA approval. HDE approval is based on demonstrating a reasonable assurance of safety and probable benefit; PMA approval is based on demonstrating a reasonable assurance of safety and effectiveness. Demonstration of probable benefit may be accomplished from the literature and may not require submission of any clinical data. If clinical data are required, they may be limited to a small single-arm study focused on feasibility and safety. This is in contrast to PMA approval, which for a significant-risk device in a new class more commonly requires large multicenter, prospective, randomized controlled trials to demonstrate safety and effectiveness. These trials can be extremely expensive and time consuming. Current trials designed to demonstrate the safety and effectiveness of a patent foramen ovale closure device for the prevention of recurrent stroke cost approximately $24 million and >4 years to complete (Table 2).8

**Discussion**

As the costs to obtain device approval continue to rise, companies (especially start-up companies devoted to developing a single device) are under extreme pressure to quickly obtain evidence of the clinical benefit of a device and its market acceptance and to generate revenues. The HUD/HDE pathway provides a way for a product to quickly enter the marketplace, allowing the company to obtain early performance data and realize revenue from device sales. For a given device, there may be multiple legitimate and distinct indications, including indications that meet the HUD criteria. Companies must choose how and when to pursue each of these indications. When contemplating the strategic use of the
HUD/HDE, one must note the following limitations. First, a strategy using the HUD/HDE pathway as a stepping stone in the development of a device intended for large markets/populations is inconsistent with the intent of this legislation and may interfere with the PMA process. Second, HDE approval restricts the commercial opportunity by confining legal marketing and promotion to the orphan indication and by limiting the amount charged for the device as detailed above. Recent changes emanating from the Medicare Modernization Act of 2003, allowing for reimbursement of routine costs for clinical trials for some IDE devices, are being implemented to relieve some of the financial burden and to encourage adequately sized trials. Third, device availability as a result of HDE approval may interfere with the ability to run large multicenter, randomized clinical trials designed to evaluate safety and effectiveness when the device is used for broader indications. The current problems of recruiting patients into clinical trials evaluating the risks and benefits of patent foramen ovale closure to prevent recurrent stroke provide a vivid illustration of the difficulties encountered in recruiting patients when a device is available for another indication. Nonetheless, for devices with multiple potential indications, it may be possible to limit these difficulties by delaying the HUD/HDE process until after completion of the enrollment phase of a PMA trial.

At the Second Dartmouth Device Development Symposium, it was the consensus among the discussants—clinical investigators, large and small medical device manufactures, senior staff from CDRH/FDA, and the venture capital community—that the HUD/HDE pathway should be reserved for true orphaned indications. This pathway should not be viewed strategically as part of the clinical development plan to access a large market.

Appendix
The Second Dartmouth Device Development Symposium Discussion Subgroup focused on HUD/HDE and included John Ahern (NMT Medical, Inc); Peter Fitzgerald, MD, PhD (Stanford University); Elisa Harvey, DVM (CDRH/FDA); Rick Hillstead (The Innovation Factory); Bob Hopkins (Lehman Brothers); Aaron V. Kaplan, MD (Dartmouth Medical School/Dartmouth-Hitchcock Medical Center); Richard, Kuntz, MD (Harvard/Brigham and Women’s Hospital); Jim O’Donnell (Cordis Corp); Jean Paul Rasschaert (Epitek, Inc); John F. Robb, MD (Dartmouth Medical School/Dartmouth-Hitchcock Medical Center); Stanton Rowe, PhD (Edwards Laboratories); Hadas Shiran, BS (Dartmouth Medical School); Charles Warden (Versant Ventures); and Jack Wennberg, MD (Dartmouth Medical School).

Acknowledgment
We thank Jason Kahn for his help in the preparation of this manuscript.

References
2. Post Safe Medical Devices Act (SMDA) of 1990, Public Law 91-4243.
3. 21 CFR 814, subpart H.
5. Section 520(m), Food, Drug and Cosmetic Act.
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