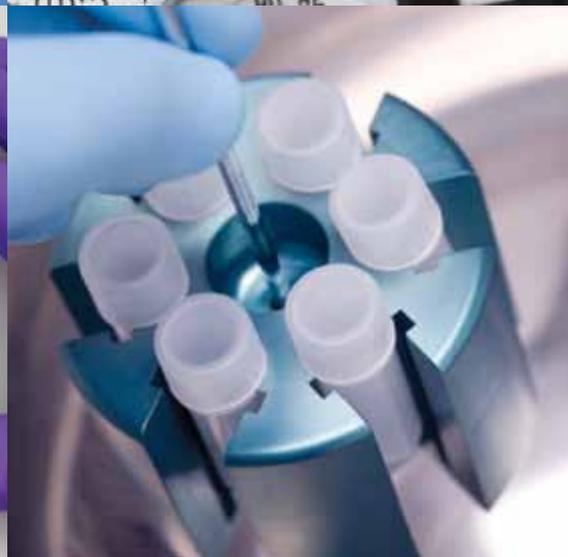
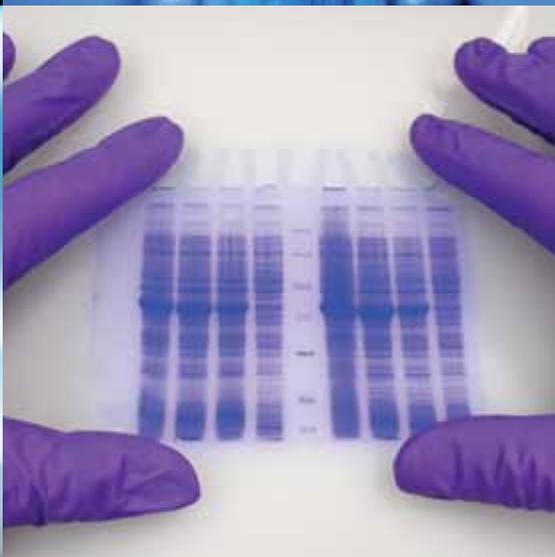
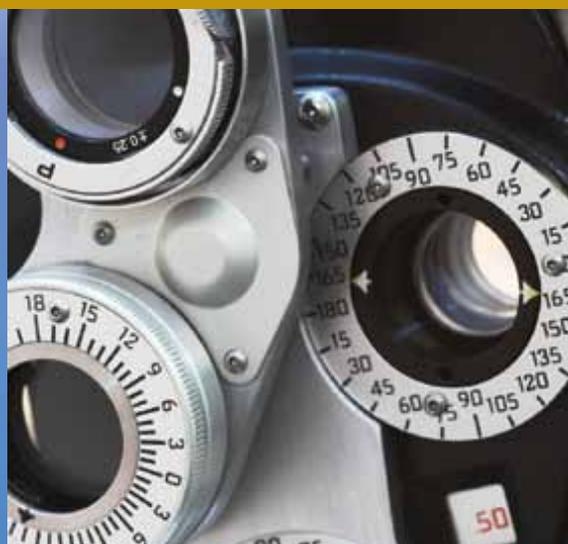
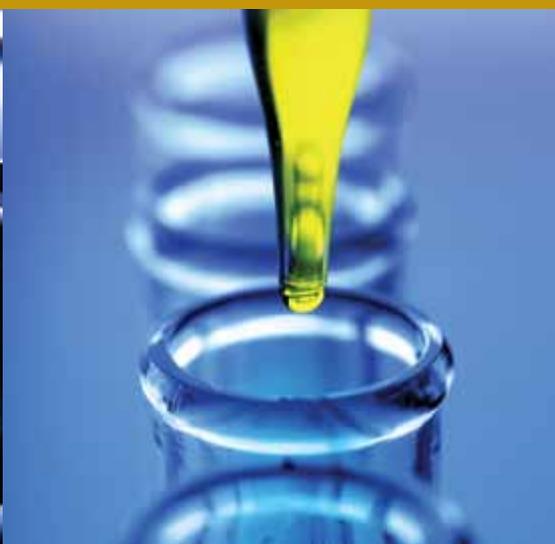




# HUDs and HDEs: Common Misconceptions and Current Challenges

By Stephen P. Rhodes and Elisa D. Harvey, MS, PhD, DVM



As former US Food and Drug Administration (FDA) employees working in the area of humanitarian use devices (HUDs) and humanitarian device exemptions (HDEs), and now regulatory consultants assisting clients interested in pursuing first an HUD designation and then an HDE for their products, we have encountered some common misconceptions regarding this regulatory concept and pathway.

## Common Misconceptions

***HUDs can be any device that fills an unmet clinical need.***

As stated on FDA's website, "The Humanitarian Use Device or HUD program was established in 1990 with passage of the *Safe Medical Devices Act* and creates an alternative pathway for getting market approval for medical devices that may help people with rare diseases or conditions. As defined by 21 CFR 814.3(n), an 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." In order to obtain HUD designation, the applicant must provide authoritative references to demonstrate that the device meets the definition of 21 CFR 814.3(n). In addition to the documentation describing the disease or condition, the applicant must also provide the proposed indications for use of the device, and the reasons why such a device is needed for the patient population." Note that the regulation contains no mention of "unmet clinical need" (<http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/DesignatingHumanitarianUseDevicesHUDs/default.htm>).<sup>1</sup> In fact, the website goes on to state specifically that "they are not patients with an unmet medical need."

Simply stated, to qualify as an HUD, a device must be shown to be applicable for a specific indication that will benefit fewer than 4,000 individuals per year in the US, regardless of whether the device fills an unmet clinical need. The first step for a sponsor wishing to market a humanitarian use device is to obtain an HUD designation from FDA's Office of Orphan Product Development (OPD) (<http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/default.htm>). Once an HUD is obtained, then a sponsor can apply for HDE approval to FDA's Center for Devices and Radiological Health (CDRH). If the HUD is not granted, then the sponsor will be unable to pursue HDE approval.

***HDEs are "easy" because no effectiveness data are required.***

This statement is frequently misinterpreted to mean that no clinical data are required. Quite the contrary is true, as the FDA website clearly explains, "An HDE application is not required

to contain the results of scientifically valid clinical investigations demonstrating that the device is effective for its intended purpose. The application, however, must contain sufficient information for FDA to determine that the device does not pose an unreasonable or significant risk of illness or injury and that the probable benefit to health outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment." Although the agency acknowledges the challenges of obtaining a large sample for a clinical study of an HUD, which by definition is applicable to a population of less than 4,000 individuals per year, there is nevertheless a requirement for demonstration of safety and probable benefit. In most cases, these can only be fully demonstrated with clinical data of some kind. A review of the Summaries of Safety and Probable Benefit from the list of FDA-approved HDEs reveals that clinical data are virtually always required to support these applications. To determine exactly what preclinical and clinical data are needed to support an HDE application for a given device, sponsors are strongly advised to contact the appropriate branch in CDRH's Office of Device Evaluation using the "pre-IDE" process to discuss their proposed testing plan.

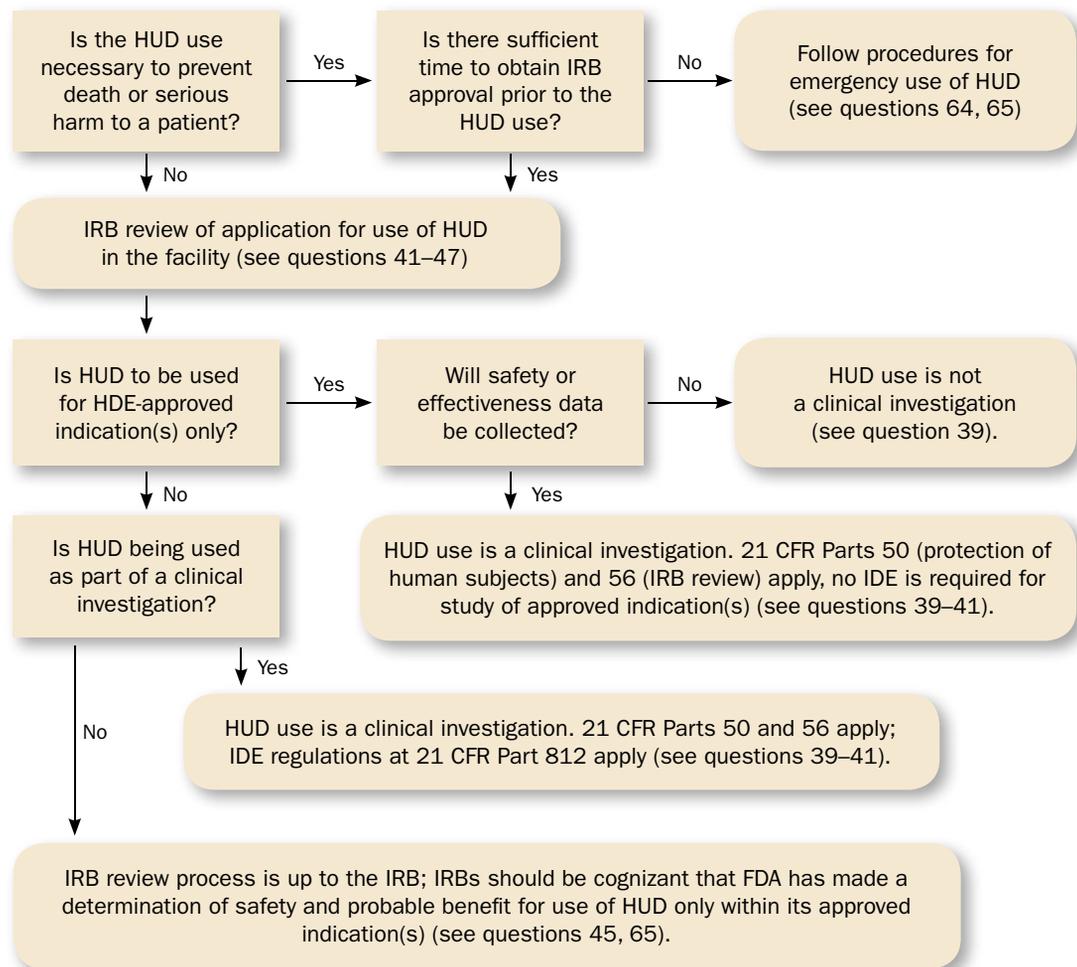
While HDEs are exempt from the effectiveness requirement, applications need to include all the other information required for premarket approval (PMA) applications. If a device is similar to an already-approved HDE, reviewing the Summary of Safety and Probable Benefit for the similar device will help formulate the appropriate safety and probable benefit information for the HDE. The summaries of all of the previously approved HDEs are available at: <http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/HDEApprovals/ucm161827.htm>.

However, many HDE applications are for novel devices. Determining the appropriate data to show that the probable benefit outweighs the risks from its use can be challenging for the HDE sponsor and the agency. Again, the pre-IDE process can be very useful as a way to engage with the review branch in an informal dialogue regarding the overall test plan.

***HUDs and HDEs are stepping stones to PMA approval.***

Although it is true that HDE approval can afford the sponsor the opportunity to pursue PMA approval for the HDE-approved indication without the need for an Investigational Device Exemption (IDE), the vast majority of FDA-approved HDEs do not, in fact, go on to obtain PMA approval. This is easily seen by reviewing the list of FDA-approved HDE devices. For that matter, there are also many more HUDs designated than there are HDEs approved. In Fiscal

Figure 1. Decision Tree for IRB Review of HUDs



2009, OOPD received 21 HUD applications and designated 10 of them. By contrast, in that same year, only four HDEs were approved.

***Use of an approved HDE will be covered by insurance.***

The Centers for Medicare and Medicaid Services (CMS) may not cover the costs associated with the use of the approved HUD. While FDA has exempted HDEs from the requirement to demonstrate a reasonable assurance of the effectiveness of the device, CMS has no such exemption from their requirements for evidence of effectiveness.

***HDEs are not marketed devices and, as such, are not subject to adverse event reporting.***

Because they require IRB approval, HDEs can be mistaken for investigational devices and exempted from adverse event reporting. However, HDEs are marketed devices, and device user facilities and manufacturers are required to submit medical device reports to FDA and to the IRB approving the use of the HUD. Manufacturers must submit reports

to FDA and the IRB whenever an 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. User facilities must submit reports to FDA, the IRB and the manufacturer whenever an HUD may have caused or contributed to a death, and must submit reports to the manufacturer whenever an HUD may have caused or contributed to a serious injury.

***A “medically plausible subset” is any smaller group of patients within a larger group with a particular medical condition.***

The primary requirement for obtaining an HUD for a device is to demonstrate with objective evidence that the device will benefit a medically plausible patient population of fewer than 4,000 individuals per year in the US. FDA’s website notes that “one aspect that has becoming increasingly difficult is if the HUD is proposed for an indication that represents a subset of a common disease or condition. In these situations, the

applicant must demonstrate that the subset is a medically plausible patient population. A medically plausible subset is considered a regulatory concept where an aspect of the HUD precludes its use in the entire disease or condition. A medically plausible subset is not a readily identifiable subset or a group of patients who meet or do not meet the inclusion and exclusion criteria for a clinical study.”

That is, a patient population cannot be “sliced and diced” down to a population size that is fewer than 4,000 per year in the US merely to allow it to meet the definition of an HUD. Instead, a sponsor of the HUD request must demonstrate that the population identified in the indication for use statement for the device is medically plausible, and that the device, by virtue of either its design or the indication, cannot be used in some larger patient population. This has been a recurring issue as acknowledged by OOPD, as many devices are submitted for HUD designation that could be used in a patient population that is smaller than 4,000 individuals per year, but could also be used in a larger population as well. Frequently, sponsors do not understand the distinction between identifying some population for which their device could provide a benefit and identifying a population smaller than 4,000 individuals per year for which the device could provide a benefit *in that population only*.

The regulatory concept of medically plausible can be simply illustrated by taking a population of any condition, for example, hypertension. The population of individuals with hypertension is very large, far exceeding the requirement of 4,000 individuals per year in the US. However, one could identify a subset of the hypertensive population that is red-haired, left-handed and under 20 years of age. This subset might well be under 4,000 individuals per year, but in no way could it be considered a “medically plausible subset,” as there is nothing about this indication or a device used to treat hypertension that would preclude use in the much wider population of patients with hypertension. It is of course an absurd example, but the logic of this concept nevertheless is applicable to identifying a medically plausible subset.

***The IRB oversight of HDE-approved devices is the same as the oversight of clinical studies.*** IRB oversight of HDE-approved devices is another area fraught with confusion. Unlike PMA-approved devices, HDE-approved devices must still have IRB oversight. IRB approval is required before an HDE-approved device may be used at any facility. However, IRBs have considerable latitude in how the device may be used at that facility. They may allow its use only within the HDE-approved indication, or they may allow its use outside the approved indication (“off-label” use). They may also require that informed consent be obtained from patients on whom

the HDE-approved device is proposed for use. Different IRBs at different facilities may have different procedures for how to oversee use of the HDE-approved devices at their sites. However, because HDE-approved devices are considered approved for marketing and are not investigational devices, IRBs do not need to make a determination as to whether they are considered a significant or nonsignificant risk. However, if a clinical investigation of an HDE-approved device within its HDE-approved indication is undertaken, IRB oversight is required, even though no IDE is required.

As the agency’s website states, “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 an HUD. Rather, the IRB may use its discretion to determine how to approve use of an 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

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precautions and evaluations, or any other criteria it determines to be appropriate.”

The agency provides a useful algorithm for how an IRB should oversee use of HDE-approved devices at its facility (see **Figure 1**).

## Recent Legislation on HDEs for Use in Pediatric Patients

The *Pediatric Medical Device Safety and Improvement Act* of 2007 provides incentives to device manufacturers to create medical devices specifically designed to meet the needs of pediatric patients, defined as patients 21 years of age or younger. The act modified HDEs so that manufacturers of devices specifically designed to meet a pediatric need could make a profit from the sale of such devices, subject to the following:

- Only original HDE applications approved for pediatric use that are approved after 27 September 2007 may be sold for profit.
- Devices that are intended to treat both a pediatric population and an adult population may be included in a single HDE application. However, the indications should specifically include use in pediatric patients and the HDE should include data supporting the safety and probable benefit of use in pediatric patients.
- The act requires the agency to designate an annual distribution number (ADN), which is the anticipated use of the product in pediatric and adult patients. The ADN must be under 4,000 and is the number of devices that may be sold for profit annually.
- The agency’s Pediatric Advisory Committee will annually review all HUDs intended for use in pediatric patients that are approved on or after 27 September 2007 to ensure that the HDE remains appropriate for the pediatric populations for which it is approved.

The intent of the HDE provisions is to provide incentives for the development of devices for use in small patient populations where otherwise a device manufacturer’s research and development costs would exceed the market for the device. During the 14 years since the effective date of the HDE regulations, the program has successfully introduced a number of important devices for treating patients with rare diseases or conditions; however, the number of HDE applications and approvals remains relatively small compared to the number of devices introduced each year. For example, during the period from 2005–09, the agency received 20 original HDE applications and approved 11 HDEs (<http://www.fda.gov/AboutFDA/CentersOffices/CDRH/CDRHReports/ucm109772.htm>). The *Pediatric Medical Device Safety and Improvement Act* of

2007 allows HDE holders of devices specifically designed to meet a pediatric need to make a profit on their sale.

A very valuable resource for information on HUDs and HDEs is the recently updated guidance document entitled, *Guidance for HDE Holders, Institutional Review Boards (IRBs), Clinical Investigators, and FDA Staff - Humanitarian Device Exemption (HDE) Regulation: Questions and Answers* (<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm110194.htm>).



### Authors

**Stephen Rhodes** joined the Biologics Consulting Group in 2010, after more than 20 years with the US Food and Drug Administration, Center for Devices and Radiological Health (CDRH). Most recently, he was the director of the Investigational Device Exemptions (IDE) and Humanitarian Device Exemptions (HDE) programs in the Office of Device Evaluation (ODE). In that position, Rhodes had oversight for policy development for all device clinical trials and also served as the CDRH Product Jurisdiction Officer, where he was responsible for CDRH recommendations to the Office of Combination Products regarding the jurisdiction of combination products as well as the CDRH recommendations to the Tissue Reference Group on products containing tissues. He also provided leadership on premarket provisions of the FDA Amendments Act of 2007, including the [clinicaltrials.gov](http://clinicaltrials.gov) databank. **Elisa Harvey, MS, PhD, DVM**, is a senior regulatory consultant at CardioMed Device Consultants, providing clinical, preclinical and regulatory consulting services for the medical device industry. Previously, Harvey worked for more than 10 years in the US Food and Drug Administration’s Office of Device Evaluation (ODE) within the Center for Devices and Radiological Health. Her most recent position at FDA was overseeing the Investigational Device Exemption (IDE) and Humanitarian Device Exemption (HDE) Programs in ODE. Here she directed regulatory policy for IDEs and HDEs, and managed ODE’s growing pre-IDE program. She holds an MS in zoology and PhD in reproductive physiology from the University of Connecticut and a DVM from Tufts University.