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Expert View

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Food and Drug Administration's Humanitarian Device Exemption Marketing Approval Pathway: Insights for Developing Devices for Rare Diseases

The Food and Drug Administration's (FDA) Humanitarian Device Exemption (HDE) is a unique marketing approval pathway for medical devices targeting diseases affecting small (rare) patient populations. In an effort to increase the utilization and success of this pathway, the FDA has analyzed data from HDE approvals from 2007 to 2015 to identify factors that have contributed to a successful HDE marketing application. There were 28 HDE approvals during the analysis period and were based on a broad range of data constituting valid scientific evidence. Most had at least one prospectively conducted clinical trial to support safety and probable benefit. An analysis of these HDE approvals demonstrates that the FDA exercises a high degree of flexibility when reviewing HDE applications. [DOI: 10.1115/1.4036333]

Introduction

Rare diseases collectively affect approximately 30 million Americans[2] [1]. However, relatively few medical devices are developed to address the needs of patients with rare diseases. To stimulate the development of such devices for these rare populations, Congress created a unique marketing approval pathway for these devices known as the HDE pathway [2]. Since the creation of this pathway 25 years ago, 69 medical devices have been approved under this pathway. In an effort to increase the utilization and success of this pathway, FDA has analyzed data from HDE approvals from 2007 to 2015 to identify factors that have contributed to a successful HDE marketing application. This article provides a review of the most recent HDE approvals and decision process and reflects the agency's current thinking on the HDE pathway.

Device developers (also referred to as sponsors) interested in bringing a device to market via the HDE pathway must first obtain a humanitarian use device (HUD) designation from FDA's Office of Orphan Products Development (OOPD) [3]. At the time a HUD designation request was submitted for each of these applications, a HUD was defined as a device intended to treat or diagnose a disease or condition that affects or is manifested in fewer than 4000 new individuals in the United States (U.S.) per year (Section 21 CFR 814.3(n)).[3] Once a HUD designation is obtained, the sponsor is eligible to submit an HDE marketing application for the HUD

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[2]This number is based on the Orphan Drug Act prevalence definition of a rare disease—affecting fewer than 200,000 individuals in the U.S.

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[3]On Dec. 13, 2016, the 21st Century Cures Act (Pub. L. No. 114–255) changed the population estimate necessary to qualify for HUD designation from "fewer than 4000" to be "not more than 8000." In addition, it requires FDA to publish guidance that defines the criteria for establishing probable benefit.

to either the Center for Devices and Radiological Health (CDRH) or Center for Biologics Evaluation and Research (CBER).

Under the HDE pathway, FDA can approve a HUD if the agency finds, among other things, that the device: (1) would not expose patients to an unreasonable or significant risk of illness or injury; and (2) that the probable benefit to health from use of the device outweighs the risk of injury or illness from its use, while taking into account the probable risks and benefits of currently available devices or alternative forms of treatment (Section 520(m)(2)(C) of the FD&C Act; 21 USC Section 360j(m)(2)(C); 21 CFR 814.104(b)(3)). The latter requirement, referred to as the "probable benefit" standard, is what primarily distinguishes the HDE marketing pathway from the traditional marketing pathway known as the Premarket Approval (PMA) pathway for high-risk medical devices for common diseases. In the PMA pathway, sponsors are required to demonstrate a reasonable assurance of safety and effectiveness [4]. The effectiveness requirement under the PMA pathway is replaced with the probable benefit standard based on the idea that establishing effectiveness for devices to treat or diagnose diseases affecting small populations is difficult. Given the probable benefit standard, HDEs are therefore subject to certain profit and use restrictions (Sections 520(m)(3)–(4) of the FD&C Act; 21 USC Section 360j(3)–(4); 21 CFR 814.104(b)(5) and 21 CFR 814.124(a)). A HUD is only eligible to be sold for profit after receiving HDE approval if the device meets the following criteria: (1) The device is intended for the treatment or diagnosis of a disease or condition that occurs in pediatric patients or in a pediatric subpopulation, and such device is labeled for use in pediatric patients or in a pediatric subpopulation in which the disease or condition occurs; or (2) the device is intended for the treatment or diagnosis of a disease or condition that does not occur in pediatric patients or that occurs in pediatric patients in such numbers that the development of the device for such patients is impossible, highly impracticable, or unsafe. If an HDE-approved device does not meet either of the eligibility criteria, then the device cannot be sold for profit. In spite of the restrictions placed on HDEs, this pathway enables sponsors to provide patients with rare diseases earlier access to life-saving medical devices while still retaining the ability to collect effectiveness data postmarket and converting the HDE approval to PMA approval.

The probable benefit standard has allowed for flexibility in device development and FDA review. To better inform device sponsors on what has been required for HDE approval, and consequently, been found to satisfy the probable benefit standard, FDA's Office of Orphan Products Development conducted an in-depth analysis of all HDE applications approved between 2007 and 2015. We described device features and examined scientific and regulatory characteristics of those approved HDE applications.

Methods

HDE approvals granted by the FDA between 2007 and 2015 were analyzed. We used the following documents for data collection: Summary of Safety and Probable Benefit (SSPB), Approved Labeling, Lead Reviewer's Review, Medical Officer's Review, and Major Deficiency Letter(s). Analyses included device characteristics, device innovation, disease and target population, clinical trials, clinical and engineering deficiencies, and flexibility in review. All data were analyzed and presented in an aggregated manner. Statistical analyses and graphing were performed using GRAPHPAD PRISM 6 software. The pediatric population in terms of medical devices is defined as individuals younger than 22 yr of age.[4] For the purpose of this analysis, the duration of use of a device referred to the duration of a single use of the device. Long-term use was defined as use $\geq$30 days, and short-term use was $<$30 days. A device labeled with repeated use over a time period of 30 days or more was categorized as short-term use device if the duration of each single use is $<$30 days. A first of a kind device was defined as a new device type, design, or indication for use that could significantly affect clinical practice, decision-making, or outcome.

Results

Characteristics of HDE Devices. From 2007 to 2015, 28 HDE devices received marketing approval (Table 1). Twenty-four (86%) were for treatment devices, while four (14%) were for diagnostic devices.[5] All of these devices were for serious or life-threatening diseases or conditions. Most were implantable (61%), long-term (64%) devices (Table 2), with cardiovascular and neurological devices accounting for 50% (14 out of 28) of the approved HDE devices.

The majority of approved HDE devices (71%) were identified by FDA as "first of a kind" devices. A first of a kind device refers to a new device type, design, or indication for use that could significantly affect clinical practice, decision-making, or outcome and may symbolize device innovation. At the time of approval, 24 (86%) of those HDE devices had not been approved for any other indication. It is not surprising that a significant number of approved HDE devices were considered innovative given the lack of precedent for rare disease-specific devices coupled with the limited knowledge of the natural history of rare diseases [5].

Rare diseases targeted by those approved HDE devices had an estimated annual incidence (i.e., number of new patients diagnosed with a disease or condition during the year) ranging from 217 to 3890 persons per year with a median of 2674 persons per year (Fig. 1). The majority of the approved HDEs targeted disease populations with an estimated annual incidence between 2000 and 4000 persons per year; six HDEs had an annual incidence of 1000 persons or less per year.

Most known rare diseases affect children [6]. Approximately one-third of the approved HDE devices are specifically labeled for pediatrics. Six of the approved HDE devices were indicated only for the adult population; three were indicated only for the pediatric population. Of the remaining 19 HDEs, age was not specified in the indications for use statement in 14 of the HDEs, while five HDEs were either indicated for adult and pediatric populations or included an age range that covered both adult and pediatric patients.

Scientific Evidence for HDE Approvals. We examined the scientific evidence that was considered by FDA during its benefit/risk determination for HDE approval. Valid scientific evidence is broadly defined in the regulations as "…evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use"[6] (21 CFR 860.7(c)(2)). Based on this definition, we categorized scientific evidence submitted in

[4]21 U.S.C. Section 360j(m)(6)(E)(i) and Section 520(m)(6)(E) of the FD&C Act.

[5]Generally, the method for estimating the affected population for HUD requests depends on whether the device is intended for therapeutic or diagnostic purposes. For therapeutic devices, the population estimate is generally the number of new patients per year diagnosed with the relevant disease or condition and eligible for treatment with the device. For diagnostic devices, the population estimate is generally the number of patients per year who would be subjected to diagnosis with the device, regardless of the outcome of the result. See 21 CFR 814.102(a)(5). For example, a diagnostic device used to screen all newborn babies for a rare disease would not qualify for the HUD/HDE marketing pathway because the number of newborn babies subjected to the device would far exceed the 4000 individuals per year limit. This definition was applicable prior to the change in the 21st Century Cures Act.

[6]Although the definition of valid scientific evidence is tied to reasonable assurance of effectiveness, we have utilized this definition for purposes of categorizing the data in HDE applications.

Table 1 List of approved HDE devices from 2007 to 2015

Device name	Indications for use	Medical specialty	Pediatric or adult	Date of approval
FENIX Continence Restoration System	This device is indicated for the treatment of fecal incontinence in patients who are not candidates for or have previously failed conservative treatment and less invasive therapy options (e.g., bulking agents, radiofrequency ablation, and sacral nerve stimulation)	Urology	Age was not specified	Dec. 18, 2015
PDGFRB FISH for Gleevec eligibility in myelodysplastic syndrome/ myeloproliferative disease (MDS/MPD)	This device is indicated for the qualitative detection of PDGFRB gene rearrangement from fresh bone marrow samples of patients with MDS/ MPD with a high index of suspicion based on karyotyping showing a 5q31∼33 anomaly. The PDGFRB FISH assay is indicated as an aid in the selection of MDS/MPD patients for whom Gleevec (imatinib mesylate) treatment is being considered. This assay is for professional use only and is to be performed at a single laboratory site	Oncology/ pathology	Age was not specified	Dec. 18, 2015
KIT D816V mutation detection by PCR for Gleevec eligibility in aggressive systemic mastocytosis (ASM)	The KIT D816V Mutation Detection by PCR for Gleevec Eligibility in Aggressive Systemic Mastocytosis (ASM). KIT D816V Mutation Detection by PCR for Gleevec Eligibility in Aggressive Systemic Mastocytosis (ASM) (referred to as the "KIT D816V assay") is an in vitro diagnostic test intended for qualitative polymerase chain reaction (PCR) detection of KIT D816V mutational status from fresh bone marrow samples of patients with aggressive systemic mastocytosis. The KIT D816V mutational assay is indicated as an aid in the selection of ASM patients for whom Gleevec® (imatinib mesylate) treatment is being considered. This assay is for professional use only and is to be performed at a single laboratory site	Oncology/ pathology	Age was not specified	Dec. 18, 2015
Osseoanchored prostheses for the rehabilitation of amputees (OPRA) device	The OPRA device is indicated for patients who have transfemoral amputation due to trauma or cancer and who have rehabilitation problems with, or cannot use, a conventional socket prosthesis. The OPRA device is intended for skeletally mature patients	Orthopedic	Adult	July 16, 2015
Kaneka Lixelle® β2-microglobulin apheresis column	This device is indicated for the treatment of patients with clinically diagnosed dialysis-related amyloidosis (DRA)	Renal	Age was not specified	Mar. 05, 2015
Impella RP System	This device is indicated for providing circulatory assistance for up to 14 days in pediatric or adult patients with a body surface area $\geq$1.5 m^2 who develop acute right heart failure or decompensation following left ventricular assist device implantation, myocardial infarction, heart transplant, or open-heart surgery	Cardiovascular	Both	Jan. 23, 2015
Barostim Neo® Legacy System	This device is indicated for use in patients with resistant hypertension who have had bilateral implantation of the Rheos® Carotid Sinus Leads Models 1010R, 1010L, 1014L, and 1014R (which have been discontinued and are obsolete) and were determined responders in the Rheos® pivotal clinical study	Cardiovascular	Age was not specified	Dec. 12, 2014
Pleximmune	This device is indicated for: The Pleximmune™ test is intended to be performed at a single laboratory to measure the CD154 expression on T-cytotoxic Memory cells (TcM) in patient's peripheral blood lymphocytes (PBL) isolated from heparinized whole blood (anticoagulant—sodium heparin). The Pleximmune™ test is a qualitative prognostic test intended to be used in patients less than 21 yr old with liver or small bowel transplantation. The Pleximmune™ test is an aid in the evaluation of the risk of acute cellular rejection (ACR) and must be used in conjunction with biopsy, standard clinical assessment, and other laboratory information	Gastroenterology/ transplant	Pediatric	Aug. 26, 2014
XVIVO Perfusion System (XPS™) with STEEN Solution™ Perfusate	The device is indicated for the flushing and temporary continuous normothermic machine perfusion of initially unacceptable excised donor lungs during which time the ex vivo function of the lungs can be reassessed for transplantation	Pulmonology/ transplant	Age was not specified	Aug. 12, 2014
Low-profile visualized intraluminal support device (LVIS and LVIS Jr.)	The device is indicated for use with bare platinum embolic coils for the treatment of unruptured, wide-neck (neck $\geq$ 4 mm or dome to neck ratio $<$ 2 mm), intracranial, saccular aneurysms arising from a parent vessel with a diameter $\geq$ 2.5 mm and $\leq$ 4.5 mm	Neurovascular	Age was not specified	July 25, 2014
Kaneka Liposorber® LA-15 System	Approval for the Kaneka Liposorber® LA-15 System. The device is indicated for use in the treatment of pediatric patients with nephrotic syndrome associated with primary focal segmental glomerulosclerosis, when: (1) standard treatment options, including corticosteroid and/or calcineurin inhibitors treatments, are unsuccessful or not well tolerated and the patient has a GFR $\geq$ ml/min/1.73 m^2; or (2) the patient is postrenal transplantation	Nephrology	Pediatric	Oct. 10, 2013

Table 1. *Continued*

Device name	Indications for use	Medical specialty	Pediatric or adult	Date of approval
Argus® II Retinal Prosthesis System	This epiretinal prosthesis is surgically implanted in and on the eye and includes an antenna, an electronics case, and an electrode array. The Argus® II Retinal Prosthesis System is intended for patients aged 25 yr and older with bare or no light perception vision caused by advanced retinitis pigmentosa	Ophthalmology	Adult	Feb. 13, 2013
Berlin Heart EXCOR® Pediatric Ventricular Assist Device (VAD)	The EXCOR is intended to provide mechanical circulatory support as a bridge to cardiac transplantation for pediatric patients. Pediatric candidates with severe isolated left ventricular or biventricular dysfunction who are candidates for cardiac transplant and require circulatory support may be treated using the EXCOR	Cardiovascular	Pediatric	Dec. 16, 2011
BSD-2000 Hyperthermia System	This device is indicated for use in conjunction with radiation therapy for the treatment of cervical carcinoma patients who normally would be treated with combined chemotherapy and radiation but are ineligible for chemotherapy due to patient related factors	Gynecology/ oncology	Adult	Nov. 18, 2011
Ovation Abdominal Stent Graft System	The TriVascular Ovation Abdominal Stent Graft System is indicated in subjects diagnosed with an aneurysm in the abdominal aorta with small aortic diameters and access vessels of less than 7 mm in diameter, and having vascular morphology suitable for endovascular repair	Cardiovascular	Age was not specified	Nov. 01, 2011 (superseded by PMA approval on Oct. 05, 2012)
NeuRx DPS™, Diaphragm Pacing System	The NeuRx Diaphragm Pacing System (DPS)™ is a percutaneous, intramuscular, diaphragm motor point stimulating device intended for use in amyotrophic lateral sclerosis (ALS) patients with a stimulatable diaphragm (both right and left portions) as demonstrated by voluntary contraction or phrenic nerve conduction studies, and who are experiencing chronic hypoventilation (CH), but not progressed to an FVC less than 45% predicted. For use only in patients 21 yr of age or older	Neurology	Both	Sept. 28, 2011
cPAX Aneurysm Treatment System	The cPAX Aneurysm Treatment System is indicated for use in the adult population (22 yr of age and older) for the treatment of wide-necked large and giant-sized cerebral aneurysms (>10) mm that require use of adjunctive assist-devices such as stents or balloons	Neurology	Adult	Apr. 01, 2011
Elana Surgical Kit	The Elana Surgical KitHUD, when connected to the Spectranetics Xenon-Chloride Laser Model CVX-300, is indicated for creating arteriotomies during an intracranial vascular bypass procedure in patients 13 yr of age or older with an aneurysm or a skull base tumor affecting a large (>2.5 mm), intracranial artery that failed balloon test occlusion, cannot be sacrificed, or cannot be treated with conventional means due to local anatomy or complexity	Neurology/ oncology	Both	Mar. 10, 2011
Medtronic Melody® Transcatheter Pulmonary Valve (Model PB10) and Medtronic Ensemble® Transcatheter Valve Delivery System (NU10)	This device is indicated for use as an adjunct to surgery in the management of pediatric and adult patients with the following clinical conditions: Existence of a full (circumferential) RVOT conduit that was equal to or greater than 16 mm in diameter when originally implanted and dysfunctional right ventricular outflow tract (RVOT) conduits with a clinical indication for intervention, and either regurgitation: >moderate regurgitation or stenosis: mean RVOT gradient >35 mm Hg	Cardiovascular	Both	Jan. 25, 2010 (superseded by PMA approval on Jan. 27, 2015)
Reclaim™ Deep Brain Stimulation for Obsessive Compulsive Disorder (OCD) Therapy	This device is indicated for bilateral stimulation of the anterior limb of the internal capsule, AIC, as an adjunct to medications and as an alternative to anterior capsulotomy for treatment of chronic, severe, treatment-resistant obsessive compulsive disorder (OCD) in adult patients who have failed at least three selective serotonin reuptake inhibitors (SSRIs)	Neurology	Adult	Feb. 10, 2009
IBV® Valve System	This device is indicated to control prolonged air leaks of the lung, or significant air leaks that are likely to become prolonged air leaks, following lobectomy, segmentectomy, or lung volume reduction surgery (LVRS). An air leak present on postoperative day 7 is considered prolonged unless present only during forced exhalation or cough. An air leak present on day 5 should be considered for treatment if it is: (1) continuous, (2) present during normal inhalation phase of inspiration, or (3) present upon normal expiration and accompanied by subcutaneous emphysema or respiratory compromise. IBV® Valve System use is limited to 6 weeks per prolonged air leak	Pulmonology	Age was not specified	Oct. 24, 2008
INFUSE/MASTERGRAFT™ Posterolateral Revision Device	The INFUSE/MASTERGRAFT™ Posterolateral Revision Device is indicated for the repair of symptomatic, posterolateral lumbar spine pseudarthrosis. This device is intended to address a small subset of patients for whom autologous bone and/or bone marrow harvest are not feasible or are not expected to promote fusion. These patients are diabetics and smokers. This device is indicated to treat two or more levels of the lumbar spine	Orthopedics	Adult	Oct. 10, 2008. This device has been withdrawn at the request of the sponsor effective Mar. 23, 2010

Table 1. *Continued*

Device name	Indications for use	Medical specialty	Pediatric or adult	Date of approval
Levitronix Centrimag® Right Ventricular Assist System (RVAS)	This device is indicated for temporary circulatory support for up to 14 days for patients in cardiogenic shock due to acute right ventricular failure	Cardiovascular	Age was not specified	Oct. 07, 2008
NeuRx RA/4	This device is indicated for use in patients with stable, high spinal cord injuries with stimulatable diaphragms, but lack control of their diaphragms. The device is indicated to allow the patients to breathe without the assistance of a mechanical ventilator for at least four continuous hours a day. For use only in patients 18 yr of age or older	Neurology	Both	June 17, 2008
Epicel® (cultured epidermal autografts)	The device is indicated for use in patients who have deep dermal or full thickness burns comprising a total body surface area of greater than or equal to 30%. It may be used in conjunction with split-thickness autografts, or alone in patients for whom split-thickness autografts may not be an option due to the severity and extent of their burns. Jurisdiction for this product has been transferred to CBER	Dermatology	Age was not specified	Oct. 25, 2007
ENTERPRISE Vascular Reconstruction Device and Delivery System	Use with embolic coils for the treatment of wide-neck, intracranial, saccular, or fusiform aneurysms arising from a parent vessel with a diameter of ≥ 3 mm and ≤ 4 mm. Wide-neck is defined as having a neck width ≥ 4 mm or a dome-to-neck ratio <2	Neurology	Age was not specified	May 08, 2007
Onyx® Liquid Embolic System (Onyx® HD-500, Model 105-8101-500	Treatment of intracranial, saccular, sidewall aneurysms that present with a wide-neck (≥ 4 mm) or with a dome-to-neck ratio <2 that are not amenable to treatment with surgical clipping	Neurology	Age was not specified	Apr. 11, 2007
Fujirebio Mesomark™ Assay	The Fujirebio Diagnostics, Inc. (FDI) MESOMARK™ is an enzyme linked immunosorbent assay (ELISA) for the quantitative measurement of soluble mesothelin related peptides (SMRP) in human serum. Measurement of SMRP may aid in the monitoring of patients diagnosed with epithelioid or biphasic mesothelioma. MESOMARK™ values must be interpreted in conjunction with all other available clinical laboratory data	Oncology/ immunology	Age was not specified	Jan. 24, 2007

approved HDE applications into four levels: clinical experience only, retrospective analysis only, single pivotal prospective clinical trial, and two or more prospective clinical trials (Tables 3 and 4). All 28 HDE approvals included some level of clinical data. The majority of approved HDE devices (19 devices, 68%) had at least one prospectively conducted clinical trial, among which 15 devices had one prospective clinical trial and four devices had two prospective clinical trials. The remaining approved HDE devices either had systematically conducted retrospective analyses of existing clinical data (seven devices, 25%) or relied on clinical experience (two devices, 7%) such as published case reports or compassionate use cases of the device.

All 19 approved HDEs with at least one prospectively conducted clinical trial were for treatment devices, not diagnostic devices. Approval of the HDEs for diagnostic devices were largely based on prespecified, FDA agreed upon analyses of previously banked sample sets, and existing clinical data. Those data as well as evaluations of analytical (bench) studies provided a reasonable assurance of safety and probable benefit that the devices could be used to inform treatment decisions or identify those patients who would be eligible for specified treatment options.

Of the 19 approved HDEs with clinical trials, 17 were nonrandomized trials and 16 were single-arm trials. Three devices

Table 2 Device description

	# of HDE approvals (out of 28)	% of HDE approvals
Device category		
Treatment	24	86
Diagnostics	4	14
Implantable	17	61
Nonimplantable	11	39
Short-term	10	36
Long-term	18	64
First of a kind device		
Yes	20	71
No	8	29
Approved/cleared for other indications at the time of HDE approval		
Yes	4	14
Under PMA	2	
Under HDE	1	
Under 510(k)	1	
No	24	86

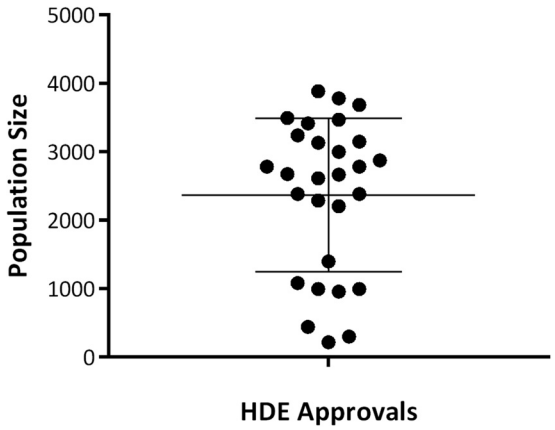

Fig. 1 Distribution of population estimate of HDE approvals

Table 3 Level of evidence of HDE approvals

	# of total HDE approvals	# of treatment HDE approvals	# of diagnostic HDE approvals
Level of evidence ($n = 28$)			
Clinical experience only	2	2	0
Retrospective analysis only[a]	7	3	4
Single prospective trial	15	15	0
Two or more prospective trials	4	4	0

[a]Note that the retrospective analysis only group includes the four approved HDEs for diagnostic devices that were largely based on prespecified, FDA agreed upon analyses of previously banked sample sets and existing clinical data.

Table 4 Overview of HDE approvals with prospective clinical trials[a]

	# of HDE approvals	% of HDE approvals
Study design ($n = 19$)		
Parallel groups	3	16
Single-arm	16	84
Randomized	2	11
Nonrandomized	17	89
Blinded	0	0
Open-label	19	100
Controls ($n = 19$)		
Concurrent control	3	16
Within subject control	3	16
Historical control	4	21
No control	9	47
Study sites ($n = 19$)		
Multicenter	16	84
Single-center	3	16
U.S. sites only	7	37
Foreign sites only	3	16
Both U.S. and foreign sites	9	47

[a]Of the HDEs approved from 2007 to 2015, only those for treatment devices were supported by a prospective clinical trial.

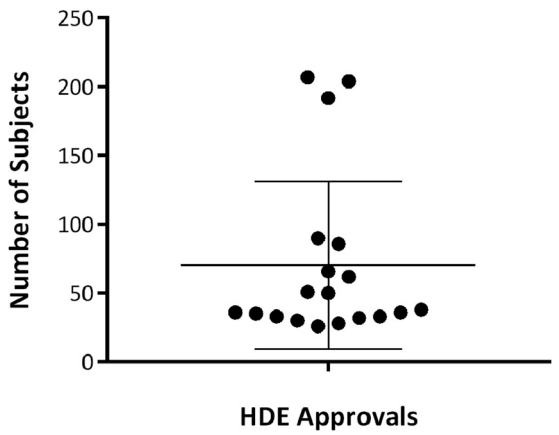

Fig. 2 Distribution of the number of subjects enrolled in HDE clinical trials

had parallel-group trials. The majority of the clinical trials had a comparator group including concurrent control (three devices), within subject control (three devices) and historical control (four devices). Trials that did not have a comparator group (nine devices) had predetermined performance criteria or other goals. Sixty-eight percent of approved HDEs with clinical trials, therefore, either had no control group or relied on a historical control. Primary safety endpoints were typically defined as rate of serious adverse events; however, probable benefit endpoints varied based on the targeted rare disease.

Of the 19 approved HDE devices with at least one clinical trial, 16 were multicenter trials. Nine devices had study sites both in the U.S. and outside the U.S. This finding is not surprising, considering that rare disease patient populations are very small and most, if not all, are geographically dispersed. Three devices were approved utilizing clinical trials conducted solely outside the U.S., and seven devices were approved utilizing clinical trials conducted only in the U.S.

The number of subjects enrolled in clinical trials ranged from 26 to 207 with an average of 70 subjects and a median of 38 subjects (Fig. 2). Trials in 16 of the 19 HDEs enrolled less than 100 subjects. Given the small patient populations involved, it is not surprising that the average number of subjects enrolled in HDE device trials is smaller than the reported number of participants enrolled in PMA trials. For example, in high-risk cardiovascular PMA device trials, the average number of participants was 308 which constitutes a fourfold difference in enrollment[7] [7]. In contrast, the average clinical trials for drugs targeting common diseases enrolled approximately ten times as many subjects as drug trials for rare diseases [8].

Common Deficiencies in HDE Applications. In order to identify if any common issues were associated with HDE applications, we reviewed those HDE applications that received major deficiency letter(s) from FDA during the review process (Table 5). Major deficiencies are outstanding issues that need to be addressed by a sponsor prior to FDA determining that the HDE application can be approved [9]. We determined that 23 of the 28 HDE applications received at least one major deficiency letter. Among those, 20 were for HDE applications for treatment devices, and three were for diagnostic devices. The percentages receiving major deficiency letters were similar between the treatment HDEs (83%) and the diagnostic HDEs (75%).

These deficiencies were categorized into clinical, engineering, nonclinical, and statistical deficiencies. The most common issue observed was insufficient clinical safety information such as rate of serious adverse events. Of the 23 HDE applications that received a major deficiency letter, 20 received deficiencies related to clinical safety of the device, and 19 received deficiencies related to clinical benefit. The majority of the clinical safety and benefit deficiencies were for treatment HDE applications (19 and 16, respectively). Nonclinical deficiencies were issued to ten treatment HDE applications and included deficiencies on biocompatibility, sterilization, and toxicology. Questions regarding the statistical analyses were also raised in eight HDE applications (seven for treatment versus one for diagnostic). Engineering deficiencies were issued to 13 HDE applications and pertained to both device design (5) and engineering testing (12). The majority of the engineering deficiencies were for treatment HDE applications. Thus, even at the HDE marketing application review stage, engineering issues were still present for 46% (13 of 28 applications).

[7]We note that the article discussing strength of study evidence was limited to PMAs from high risk cardiovascular devices from January 2000 to December 2007 to support a reasonable assurance of safety and effectiveness finding.

Table 5 Common deficiencies

	# of HDE approvals	# of treatment HDE approvals	# of diagnostic HDE approvals
Received major deficiencies	23	20	3
Clinical deficiencies	23	20	3
Safety	20	19	1
Probable benefit	19	16	3
Engineering deficiencies	13	11	2
Design	5	5	0
Testing	12	10	2
Nonclinical deficiencies (biocompatibility, sterilization, and toxicology)	10	10	0
Statistical deficiencies	8	7	1

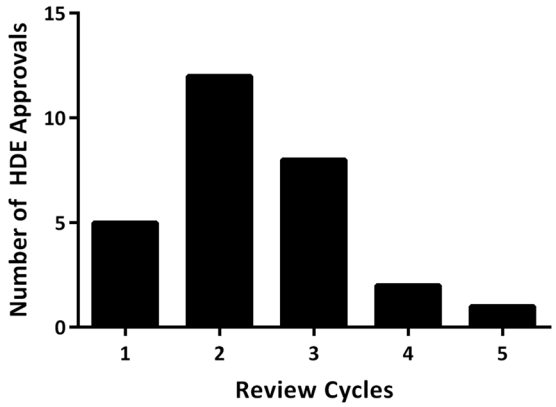

Fig. 3 HDE review cycles

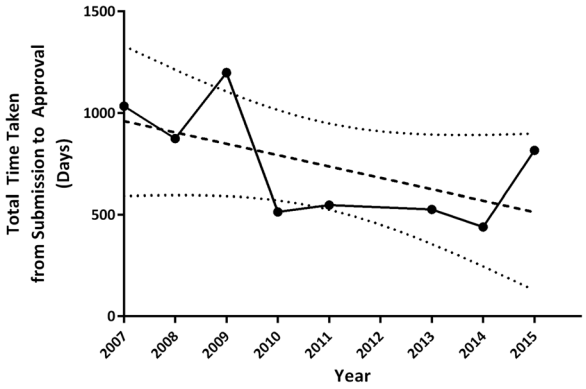

Fig. 4 Total time taken from filing of HDE application to approval: a decreasing trend

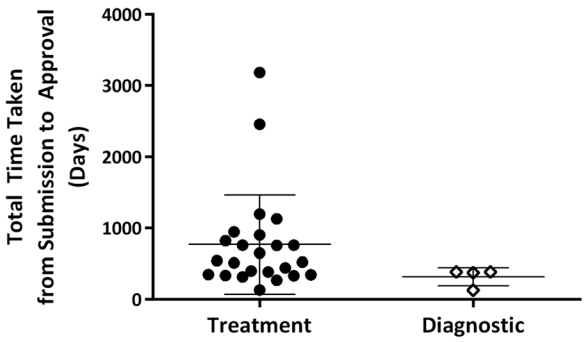

Fig. 5 Total time taken from filing of HDE application to approval: treatment versus diagnostic devices

While these issues were eventually resolved, it highlights the importance of addressing engineering issues at the earliest possible stage of device development, since device iterations occur throughout the total product lifecycle.

Flexibility in Review of HDE Devices. We used issuance of a major deficiency letter to define FDA's review cycles. If no major deficiency letter was issued, issuance of an approval letter was used to mark the end of a review cycle. Seventeen of 28 HDE applications were approved within two review cycles, and 25 of 28 were approved within three review cycles (Fig. 3). The total time taken from FDA filing of the HDE application to approval ranged from 133 days to 3184 days with a median of 480 days (Fig. 4). On average, the total time taken from FDA filing of the HDE application to approval for treatment devices was 770.9 ± 142.5 days, and it was 321.0 ± 62.7 days for diagnostic devices (Fig. 5). This time incorporates both the FDA review time and the sponsor time in providing the necessary information to establish safety and probable benefit. There appeared to be a decreasing trend in time taken from when the HDE application was received to approval date throughout the 9 years.

The small population sizes of rare diseases make it inherently difficult to conduct large, concurrently controlled clinical trials; in some cases small, single-arm studies may be the only practical option. The unique challenges of rare diseases call for flexible approaches to utilize all available scientific evidence in benefit/risk assessment. This analysis indicates that FDA has demonstrated a high degree of flexibility in its review of HDE applications. FDA has accepted a wide range of clinical evidence for approval from retrospective analyses of prior clinical studies to prospectively conducted clinical trials for HDE approvals. It is worth noting that the HDEs for the diagnostic devices were approved based on prespecified analyses utilizing patient samples from previously conducted clinical studies, which suggest flexible approaches tailored to diagnostic devices. Approximately 20% of the approved HDE applications utilized data extrapolation during review. Data extrapolation allows the use of existing clinical data from other diseases to provide insights on safety and probable benefit without creating an additional burden to sponsors or delaying patient access. FDA has also utilized postapproval requirements such as continued patient follow-up and enrollment of new subjects into postapproval studies to continue to monitor risks and benefits. These requirements are especially important for rare disease patients who often have little or no alternative treatment

options. Among the approved HDE applications evaluated, FDA required postapproval studies in 64% of cases.

Conclusion and Discussion

The HUD/HDE program provides an alternative marketing approval pathway for innovative medical devices treating or diagnosing rare diseases. The HDE devices approved from 2007 to 2015 consisted of both diagnostic and treatment devices and targeted a variety of rare diseases of both adult and pediatric patients. The most common issues associated with these HDE applications were related to clinical safety and probable benefit. Device design and engineering testing also played critical roles in the review process to assess the safety and probable benefit of these devices. Clinical trials for HDE devices were relatively small compared to those for PMA devices; most were open-label, single-arm trials. Overall, valid scientific evidence at various levels were submitted to support HDE approvals. With the ultimate goal of providing treatment options to patients with serious or life-threatening rare diseases, FDA exercised flexibility in all HDE reviews. The 21st Century Cures Act (Pub. L. No. 114–255) broadens the HUD/HDE program by increasing the population estimate requirement from "fewer than 4000" to "not more than 8000." This increase should hopefully allow the HUD/HDE pathway to facilitate a greater number of devices to market for the treatment or diagnosis of rare diseases or conditions. To best facilitate rare disease device development, sponsors should communicate with FDA early in the development process to ensure a least burdensome approach to obtaining marketing approval for these devices.

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