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# **Draft Guidance for Industry and Food and Drug Administration Staff**

## **Humanitarian Use Device (HUD) Designations**

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For questions regarding this draft document contact Mr. Eric Chen 301-796-6327, [eric.chen@fda.hhs.gov](mailto:eric.chen@fda.hhs.gov).

**U.S. Department of Health and Human Services  
Food and Drug Administration  
Office of Orphan Products Development (OOPD)  
Center for Devices and Radiological Health (CDRH)  
Center for Biologics Evaluation and Research (CBER)**

**December 2011**

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# Draft Guidance for Industry and Food and Drug Administration Staff

## Humanitarian Use Device (HUD) Designations

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1                   **Draft Guidance for Industry and**  
2                   **Food and Drug Administration Staff**

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5                   **Humanitarian Use Device (HUD)**  
6                   **Designations**

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9                   This draft guidance, when finalized, will represent the Food and Drug Administration’s (FDA’s) current  
10                  thinking on this topic. It does not create or confer any rights for or on any person and does not operate to  
11                  bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of  
12                  the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA  
13                  staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call  
14                  the appropriate number listed on the title page of this guidance.  
15

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17  
18                  **I. INTRODUCTION**

19  
20                  This guidance document is intended to assist applicants in the preparation and submission of  
21                  Humanitarian Use Device (HUD) designation requests to the U.S. Food and Drug Administration  
22                  (FDA or Agency) Office of Orphan Products Development (OOPD). It is also designed to assist  
23                  FDA reviewers in their evaluation and analysis of HUD designation requests. Topics addressed  
24                  in this guidance include: 1) demonstrating in HUD requests that the device is designed to treat  
25                  or diagnose a disease or condition that affects or is manifested in fewer than 4,000 individuals in  
26                  the United States per year, 2) how this demonstration varies depending on whether the device is  
27                  intended for therapeutic or diagnostic purposes, 3) how properties of the device may affect this  
28                  demonstration, and 4) delineating a medically plausible subset of persons with a given disease or  
29                  condition.

30  
31                  This guidance addresses only HUD designation requests. HUD designation requests are the first  
32                  step in seeking marketing approval of a HUD. This guidance does not address the second step in  
33                  this marketing approval process—namely the submission of a Humanitarian Device Exemption  
34                  (HDE) application to the Center for Devices and Radiological Health (CDRH) or to the Center  
35                  for Biologics Evaluation and Research (CBER). For more information on the preparation and  
36                  submission of HDE applications, see the FDA Guidance on *Humanitarian Device Exemption*  
37                  (*HDE*) Regulation: *Questions and Answers* (July 2010).<sup>1</sup>  
38

39                  This guidance is responsive to the congressional mandate in Section 740 for the fiscal year 2010  
40                  U.S. Appropriation Act (Agriculture, Rural Development, Food and Drug Administration, and

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<sup>1</sup> This guidance is available at  
[www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm110194.htm](http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm110194.htm).

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41 Related Agencies Appropriation Act, 2010, Public Law 111-80) dated October 21, 2009.  
42 Among other things, the congressional mandate required that the Commissioner of the Food and  
43 Drugs establish a review group within FDA to make recommendations on appropriate aspects  
44 related to rare and neglected diseases and to develop guidance document(s) based upon these  
45 recommendations.

46  
47 FDA guidance documents, including this guidance, do not establish legally enforceable  
48 responsibilities. Instead, guidances describe the Agency’s current thinking on a topic and should  
49 be viewed only as recommendations – unless specific regulatory or statutory requirements are  
50 cited. The use of the word *should* in Agency guidances means that something is suggested or  
51 recommended but not required.

52

## 53 **II. BACKGROUND**

54

55 The HUD designation program in the Office of Orphan Products Development supports the HDE  
56 provisions of the 1990 Safe Medical Devices Act (SMDA) (Public Law 101-629). See section  
57 520(m) of the Federal Food, Drug, and Cosmetic Act (FD&C Act, 21 USC §360j). As defined in  
58 21 CFR 814.3(n), a HUD is a “medical device intended to benefit patients in the treatment or  
59 diagnosis of a disease or condition that affects or is manifested in fewer than 4,000 individuals in  
60 the United States per year.” If there are questions about whether your product is subject to  
61 regulation as a medical device, you should file a request for designation under 21 CFR part 3  
62 prior to a HUD designation request.

63

64 Devices that receive HUD designation may be eligible for marketing approval under an HDE  
65 application. An HDE application is a premarketing application that is similar to a premarket  
66 approval (PMA) application in that the applicant must demonstrate a reasonable assurance of  
67 safety, but in an HDE application the applicant seeks an exemption from the PMA requirement  
68 to demonstrate a reasonable assurance of effectiveness. A device that has received HUD  
69 designation is eligible for HDE approval if, among other criteria, the probable benefit to health  
70 from use of the device outweighs the risk of injury or illness from its use, taking into account the  
71 probable risks and benefits of currently available devices or alternative forms of treatment.  
72 Section 520(m) of the FD&C Act; 21 CFR 814.104(b)(2).<sup>2</sup> FDA approval of an HDE  
73 application authorizes the applicant to market the device. This marketing is subject to certain  
74 profit and use restrictions set forth in section 520(m) of the FD&C Act. For more information on  
75 HDE applications and profit and use restrictions, see the FDA Guidance on *Humanitarian*  
76 *Device Exemption (HDE) Regulation: Questions and Answers* (July 2010).<sup>3</sup>

77

78 Although a HUD designation from the OOPD is a prerequisite for submitting an HDE marketing  
79 application to CDRH or CBER, it does not by itself guarantee approval of the HDE application.  
80 21 CFR 814.102(b).

81

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<sup>2</sup> Additionally, to be eligible for HDE approval, the applicant must certify that no comparable device, other than another device approved under HDE or a device approved under an Investigational Device Exemption (IDE), is available to treat or diagnose the disease or condition, and explain why the device would not be available for the indication in question without the HDE approval. Section 520(m) of the FD&C Act; 21 CFR 814.104(b)(2).

<sup>3</sup> This guidance is available at

[www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm110194.htm](http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm110194.htm).

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82 The required contents of a HUD designation request are set forth in 21 CFR 814.102 and  
83 described in detail in Section III of this guidance document. Once a HUD designation request is  
84 ready for submission to OOPD, the applicant should send two signed and dated submissions (the  
85 original and a copy) to the address below.

86  
87 Office of Orphan Products Development  
88 Food and Drug Administration  
89 10903 New Hampshire Avenue  
90 WO32-5271  
91 Silver Spring, MD 20993  
92

93 Of these submissions, at least one should be a hardcopy and the other may be an electronic CD  
94 with a signed, identical version of the hardcopy. If questions arise regarding HUD designation  
95 requests or general questions related to the program, the FDA Office of Orphan Products  
96 Development may be contacted at 301-796-8660.

97  
98 Upon receipt of a HUD designation request, the OOPD will issue an acknowledgement letter to  
99 the applicant and assign a reference number for any future correspondence related to that  
100 designation request. The review process for a HUD request takes 45 calendar days from the date  
101 of receipt by the OOPD. Within this 45-day timeframe the OOPD may approve the request,  
102 request additional information (the receipt of additional information from the applicant will  
103 trigger a new 45-day review clock), or disapprove the request. 21 CFR 814.102(b).

104  
105 If the HUD designation request is approved, the applicant becomes eligible to submit an HDE  
106 marketing application to the appropriate assigned center (CDRH or CBER). The HDE  
107 application must include a copy of or reference to the OOPD's HUD designation letter for the  
108 device. 21 CFR 814.104(b)(1).<sup>4</sup> A HUD designation is a prerequisite to submitting an HDE  
109 marketing application; it is only one of many required elements of an HDE application. 21 CFR  
110 814.104. Receipt of a HUD designation does not guarantee that the HDE marketing application  
111 will be approved.

112  
113

### **III. CONTENTS OF HUD DESIGNATION REQUESTS**

114

115 As set forth in 21 CFR 814.102, a HUD designation request includes the following:

116  
117

- 118 (1) A statement that the applicant requests HUD designation for a rare disease or condition or  
119 a specifically identified valid subset of a common disease or condition (see Section  
120 III.C).
- 121 (2) The title, name, address, and telephone number of the applicant and the primary contact  
122 person(s). An email address for the primary contact person(s) is recommended.
- 123 (3) A description of the rare disease or condition for which the device is to be used, ideally  
124 with particular emphasis on the specific aspects of the disease or condition relevant to the

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<sup>4</sup> We encourage applicants to submit a copy of the designation letter with their HDE application, rather than just a reference to this letter.

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125 functionality of the device, as well as the proposed indication(s) for use of the device and  
126 the reasons why such therapy is needed.

127 ○ If the proposed indication(s) is for a rare subset of a common disease or condition  
128 that affects or is manifested in 4,000 or more individuals in the United States per  
129 year, there should be a demonstration that this subset is medically plausible (see  
130 Section III.C).

131 (4) A description of the device and a discussion of the scientific rationale for the use of the  
132 device for the rare disease or condition (see Section III.D).

133 (5) Documentation, with appended authoritative references, that the device is designed to  
134 treat or diagnose a disease or condition that affects or is manifested in fewer than 4,000  
135 people in the United States per year (see Sections III.B and III.E).

136 ○ If the device is intended for diagnostic purposes,<sup>5</sup> including devices intended to  
137 assess the state of a patient's health, the population documentation must  
138 demonstrate that fewer than 4,000 patients per year would be subjected to  
139 diagnosis by the device for the disease or condition in the United States. 21 CFR  
140 814.102(a)(5). This population estimate would include all patients who would be  
141 tested with the diagnostic device annually, including all who test positive or  
142 negative for the disease or condition (see Section III.B.2).  
143

144 We recommend that applicants include a cover letter in their HUD designation requests  
145 containing a statement that they request HUD designation for a rare disease or condition or a  
146 specifically identified valid rare subset of a common disease or condition. For the remaining  
147 information listed below, we recommend that applicants include a table of contents, with  
148 pagination, identifying information in the following order:  
149

- 150 • title, name, address, telephone number, and email address of the applicant and  
151 primary contact person(s);
- 152 • description of the rare disease or condition, including, if relevant, adequate  
153 documentation of a medically plausible subset of a common disease or condition;
- 154 • proposed indication(s) for use of the device;
- 155 • description of the device and the scientific rationale for its use as proposed;
- 156 • population determination;
- 157 • bibliography;
- 158 • copies of all cited references separated by tabs; and
- 159 • appendices, if applicable.  
160

161 Below, we provide clarity on particular elements of HUD designation requests that have  
162 historically caused confusion among applicants. In particular, we focus on the description of the  
163 disease or condition, population determinations, medically plausible subsets, device description,  
164 scientific rationales, and supporting documentation.  
165

**A. Description of the Disease or Condition**  
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<sup>5</sup> See, for example, 21 CFR 809.3(a) (definition of *in vitro* diagnostic products).

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168 A HUD designation request must include a description of the rare disease or condition for  
169 which the device is to be used. 21 CFR 814.102(a)(3). Ideally, the description of the rare  
170 disease should focus on specific aspects of the disease or condition relevant to the  
171 functionality of the device, as well as any information that assists in defining the patient  
172 population.

173  
174 The OOPD designates a device for a rare disease or condition, not for a specific  
175 indication. Accordingly, the main question at this stage of the HUD designation process  
176 is “what disease or condition is the device designed to treat or diagnose?” – not what  
177 labeling the applicant may eventually propose at the HDE approval stage. It is not  
178 uncommon for the scope of a HUD designation to be broader than the indication(s) for  
179 which the applicant may eventually seek marketing approval. For example, at the HUD  
180 stage a device may be designated for treatment of fetal bladder obstruction, but at the  
181 HDE stage the device may be approved only for treatment of fetal bladder obstruction in  
182 fetuses of 18 to 32 weeks gestational age.

183  
184 The OOPD independently evaluates the disease or condition that the device is designed to  
185 treat or diagnose. Based on this independent evaluation, the OOPD may determine that  
186 the disease or condition that the device is designed to treat or diagnose is broader than, or  
187 different from, that proposed by the applicant. For example, an applicant may state in a  
188 HUD designation request that a device (a polymer) treats lytic lesions due to multiple  
189 myeloma. The OOPD may believe, based on information about the device, that the  
190 disease or condition treated by the device is lytic lesions regardless of cause (e.g., due to  
191 multiple myeloma, bone metastasis, or hemangioma). In this case, the OOPD would  
192 request that the applicant clarify why lytic lesions due to multiple myeloma, for the  
193 purpose of this HUD designation request, represent a different disease or condition from  
194 other lytic lesions.

195  
196 If the OOPD determines that the disease or condition that the device is designed to treat  
197 or diagnose affects or is manifested in 4,000 or more patients per year in the United  
198 States or if the population estimate is not appropriate, to be eligible for HUD designation,  
199 the applicant would have to demonstrate that either: (a) the disease or condition that is  
200 the subject of the HUD request is a different disease or condition than that identified by  
201 the OOPD (e.g., by showing that lytic lesions from multiple myeloma are a different  
202 disease or condition from lytic lesions due to other causes, such as metastatic disease); or  
203 (b) the disease or condition that is the subject of the HUD request is in fact a medically  
204 plausible subset of a common disease or condition, based on intrinsic features of the  
205 device (e.g., some feature of the device would preclude its use in lytic lesions from all  
206 causes). See Section III.C, below, for more information on medically plausible subsets.

207  
208 See also “Simplified HUD Decision Flowchart,” below, that describes the OOPD review  
209 process for a HUD designation request.<sup>6</sup>  
210

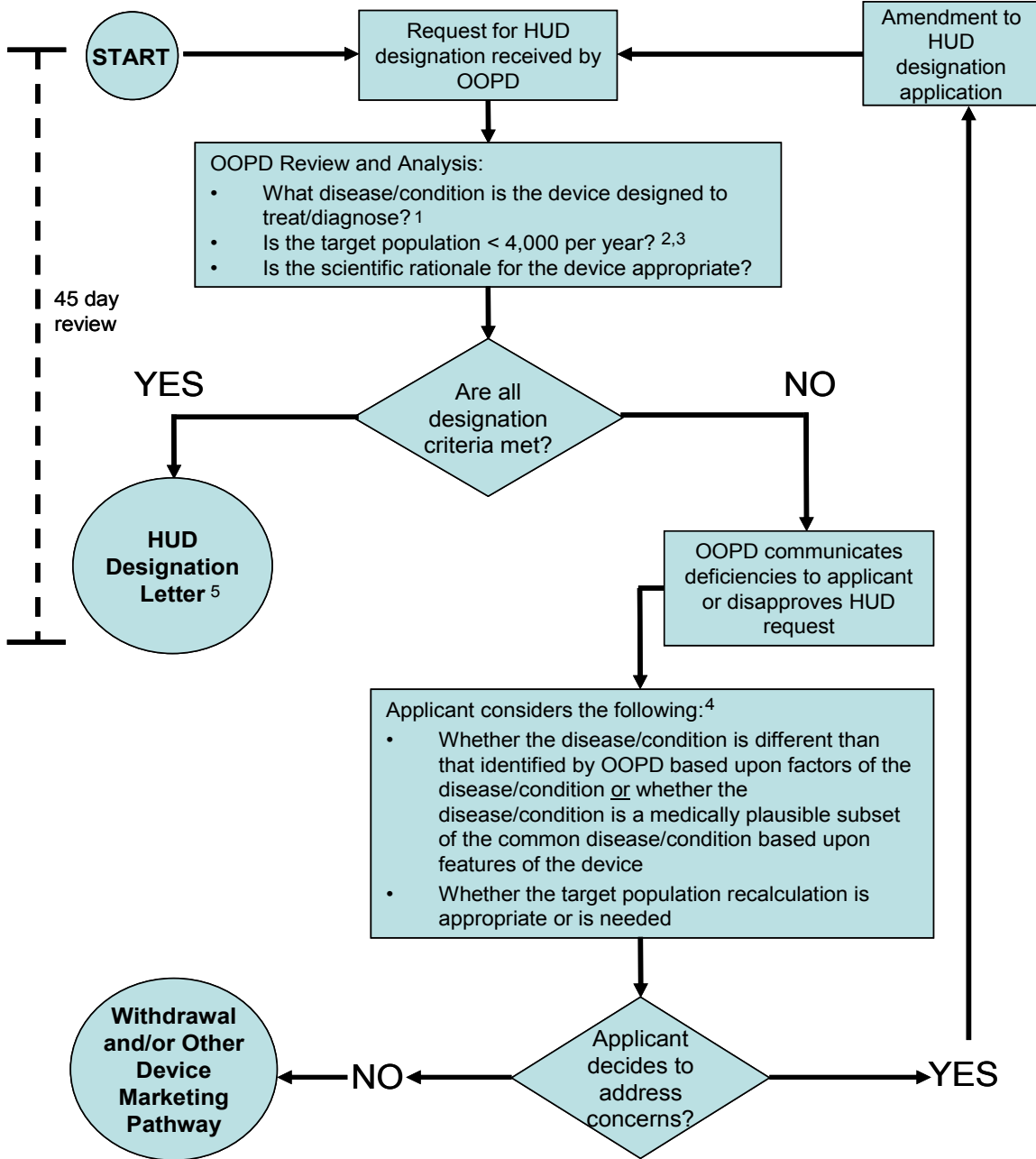
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<sup>6</sup> The “Simplified HUD Decision Flowchart” outlines the OOPD review process for a HUD designation request. It shows that the initial review by OOPD is done by identifying the disease or condition, the target population, and reviewing the scientific rationale for the device. OOPD has 45 days to review the submission and once that review has been completed, official communication is provided to the applicant.

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**Simplified HUD Decision Flowchart**



1. OOPD designates a device for a disease/condition, not for a specific indication
2. Therapeutic devices are eligible when the disease/condition affects or is manifested in fewer than 4,000 individuals/year in the United States
3. Diagnostic devices are eligible when the number of individuals that would be subjected to diagnosis by the device is fewer than 4,000 individuals/year in the United States
4. During this time, applicants may choose to have open discussion regarding concerns with OOPD
5. Applicant may submit HDE marketing application after receiving the HUD designation letter

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**B. Population Determinations**

Applicants should identify in HUD designation requests whether the device is intended for therapeutic or diagnostic purposes. As discussed more below, this information is important in OOPD’s review of an applicant’s population determination.

**B.1 Therapeutic Devices – Annual Incidence of the Disease or Condition in the United States**

Therapeutic devices eligible for HUD designation are devices designed to treat a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year. 21 CFR 814.3(n). In seeking HUD designation for these devices, it is important to understand the difference between disease *prevalence* and *incidence*, as well as how these concepts affect HUD designation requests.

*Prevalence* is generally understood as the total number of patients with a disease or condition in the population at a given time (e.g., point prevalence). *Incidence* is generally understood as the number of new patients diagnosed with a disease or condition during a particular time period, such as annually (e.g., annual incidence). As described in the preamble to the 1996 Final Rule on HUD designations, FDA added the qualifying phrase “per year” to the regulation (“4,000 individuals in the United States”) in an attempt to clarify that it interprets the statutory provision not as point prevalence, but as annual incidence.<sup>7</sup>

For therapeutic devices, incidence demonstration in HUD designation requests generally means the number of new patients per year who are diagnosed with the disease or condition and would be eligible for treatment with the device, given the characteristics of the disease or condition and the properties of the device.

An example of an approved HUD designation request was for the Harrison Fetal Bladder Stent, which was later approved under HDE H960001 on February 14, 1997 for fetal urinary tract decompression following the diagnosis of fetal post-vesicular obstructive uropathy in fetuses of 18 to 32 weeks gestational age. In evaluating the HUD request, the OOPD determined that the incidence of the relevant disease or condition – fetal post-vesicular obstructive uropathy, regardless of gestational age<sup>8</sup> – was fewer than 4,000 patients per year.

Some incidence demonstrations can be complicated, depending on the device and the disease or condition in question. For example, if a device is designed to treat only recurrent events in a patient (i.e., two or more events, such as cerebrovascular accidents),

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<sup>7</sup> 21 Fed. Reg. 33232, 33233 (June 26, 1996). As FDA described in this rulemaking, this interpretation serves the primary purpose of section 520(m) of the FD&C Act, to provide an incentive for the development of devices to be used in the treatment or diagnosis of diseases or conditions that affect small patient populations. Adopting a point prevalence definition would have been considerably more restrictive and would have provided less of an incentive for the development of such devices.

<sup>8</sup> As described earlier in this document, it is not uncommon for the HUD-designated disease or condition to be broader than the specific indication for which the device may eventually be approved at the HDE stage.

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252 then the incidence estimate should include not only those patients who experienced their  
253 first and second events in the given year, but also patients who experienced an initial  
254 event in prior years and then experienced a recurrent event in the given year.  
255

**B.2 Diagnostic Devices – Patients Per Year Who Would be Subjected to  
Diagnosis by the Device in the United States (Regardless of Test  
Result)**

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259  
260 As stated in 21 CFR 814.102(a)(5), the population determination for diagnostic devices  
261 depends on the number of patients per year who would be subjected to diagnosis by the  
262 device in the United States. This calculation includes not only those who test positive for  
263 the disease or condition, but also those who test negative for the disease or condition.  
264 Thus, a diagnostic device would be ineligible for HUD designation even if it is intended  
265 to diagnose a rare disease or condition if 4,000 or more patients per year would be tested  
266 with the device – regardless of whether the test result is positive or negative.  
267

268 The number of patients per year who would be subjected to diagnosis with the device  
269 depends on the disease or condition the device diagnoses and the circumstances for use.  
270 For example, the number of patients would differ depending on whether the diagnostic is  
271 an initial diagnostic or screening test used to diagnose or screen a population, a  
272 confirmatory test used to confirm the diagnosis of individuals who have already screened  
273 positive for the disease or condition, a treatment guide used to help select or exclude a  
274 given therapy, or a monitoring test used to monitor disease progression.  
275

276 An example of a diagnostic device that would not qualify for HUD designation is a  
277 device used to screen all newborn babies to identify certain serious or life-threatening  
278 conditions before symptoms begin. Even if the serious life-threatening disease or  
279 condition ultimately affects less than 4,000 babies/patients in the United States per year,  
280 because all newborn babies are subjected to the screening test, the diagnostic device is  
281 not eligible for HUD designation.  
282

283 However, an example of a diagnostic device that may qualify for a HUD designation is a  
284 device that identifies a specific gene rearrangement in a rare malignancy. In this  
285 example, the incidence of the rare malignancy affects fewer than 4,000 new cases per  
286 year. Because less than 4,000 patients per year in the United States are potentially going  
287 to use the diagnostic device to identify the specific gene sequence, the diagnostic device  
288 may qualify for HUD designation.  
289

**B.3 Devices Intended For Repeat or Multiple Use**

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291  
292 We recognize that an individual may use a device more than once a year. For example, a  
293 device intended for repeat or multiple uses could be a device implanted in more than one  
294 organ or multiple devices implanted in a single organ. HUD designations for therapeutic  
295 devices depend on the total number of new patients who would be eligible for the device  
296 in a given year– not on the total number of devices expected to be used in a given year.  
297 HUD designations for diagnostic devices depend on the total number of patients

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298 subjected to diagnosis by the device in a given year – not on the total number of devices  
299 expected to be used in a given year.<sup>9</sup>

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#### **C. Medically Plausible Subset**

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If the subject of a request for HUD designation is a subset of a common disease or condition – a common disease or condition is defined for HUD purposes as having an annual incidence of 4,000 or more people in the United States – then the request should include a demonstration that this subset is medically plausible. 21 CFR 814.102(a)(3). Medically plausible subsets are often referred to as “orphan subsets.”

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“Medically plausible subset” or “orphan subset” is a regulatory term used to describe a situation where the incidence of a disease or condition is 4,000 or more patients per year in the United States, but because a product can only be used in a smaller subset of people with the common disease or condition, it qualifies for HUD designation. A medically plausible subset must be based on some feature of the device (i.e., mode of action, adverse event profile, etc.) that actually precludes its use in the treatment of patients outside the smaller subset of individuals.

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Using stroke as an example, recurrent stroke where drug therapy has failed could represent a medically plausible subset of stroke for some devices. HUD designation could be granted, for example, if the device, such as an implantable device, is known to have a serious adverse event profile. This is because the implantable device with a serious adverse event profile is not likely to be used after just one stroke when therapies with fewer risks are available. The serious adverse event profile may preclude use of the implantable device as a first line treatment. Alternatively, a recurrent stroke population would not likely be considered a medically plausible subset of the stroke population for a device that has a less serious adverse event profile (e.g., a non-invasive device); this is because the device may be appropriately used in the general stroke population.

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The fundamental principle required to understand the concept of a medically plausible or orphan subset is that a medically plausible subset cannot be considered without reference to the device that is the subject of the request for HUD designation, and the feature of the device (i.e., mode of action, adverse event profile, etc.) that precludes its use in the treatment of patients outside the smaller subset of individuals.

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The term “medically plausible subset” does not mean *any* readily identifiable patient population subset (note that a readily identifiable patient population would not require reference to a device). There should be justification as to why the device could not be used to treat or diagnose all remaining persons with the disease or condition. Examples of what medically plausible subset does *not* mean in this context include:

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341

- An applicant’s intention to study or use the device in a certain limited population of patients with a common disease or condition unless it would be medically

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<sup>9</sup> See 21 CFR 814.126(b)(1)(iii).

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342 inappropriate to evaluate or use the same device in the remaining population with  
343 the disease or condition.

344 • Proposed restrictive labeling for the device absent medical or scientific  
345 justification for that restriction. For example, restricting the indication to a subset  
346 of patients with a particular pathohistologic grade or clinical stage of a specific  
347 malignancy does not render the subset “medically plausible” absent some reason  
348 to believe the device cannot be used to treat all remaining patients with the  
349 malignancy regardless of disease grade or stage.

350 • Patients who meet or do not meet the inclusion or exclusion criteria of a given  
351 clinical trial, absent further justification.

352 • Patients with an unmet medical need, without further justification.

353 • The current “standard of care” may not represent a medical plausible subset  
354 because the standard of care evolves over time and the device may be appropriate  
355 to be used in the larger target population.

356

357 In general, the OOPD designates a device for the treatment or diagnosis of a disease or  
358 condition that affects or is manifested in fewer than 4,000 individuals in the United States  
359 per year. This is true even if the applicant may ultimately pursue marketing approval of  
360 the device for an even narrower indication.

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**D. Device Description and Scientific Rationale for its Proposed Use**

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**D.1 Device Description**

The description of the device should include adequate details to fully describe the device under consideration, i.e., a comprehensive list and description of all components of the device with relevant dimensions, reagents, and/or specifications noted. Drawings or photographs are encouraged, as well as a description of the mechanistic and operative aspects of the device.

**D.2 Scientific Rationale**

The scientific rationale supporting use of the device for the rare disease or condition, or a medically plausible subset of a common disease or condition (see Section III.C), should contain all preclinical, clinical, published, or proof-of-principle data pertaining to the device as applicable – whether positive, negative, or inconclusive. It should be noted that the preclinical information on whether a device has been verified and validated against the proposed engineering design specifications is reviewed in the HDE marketing application and not in the HUD designation request.

**E. Supporting Documentation**

The applicant must include documentation, with appended references, to demonstrate that the device is intended to treat or diagnose a disease or condition that affects or is manifested in fewer than 4,000 people per year in the United States. For diagnostic

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387 devices, this documentation must demonstrate that fewer than 4,000 patients per year  
388 would be subjected to diagnosis by the device in the United States. 21 CFR  
389 814.102(a)(5). Authoritative references in this context include “specialized medical  
390 journals, textbooks, specialized medical society proceedings, or governmental statistics  
391 publications.” 21 CFR 814.102(a)(5).

392  
393 We recommend including in HUD designation requests all relevant documentation on the  
394 incidence determination – whether supportive, non-supportive, or inconclusive. If  
395 inadequate literature or other resources exist to document the annual incidence of the  
396 disease or condition, the applicant should document the effort to obtain such information  
397 and may then provide a credible incidence estimate through the use of appropriate  
398 research, surveys, or consultation with independent experts in the relevant field.  
399 Generally, for an estimate from experts to be considered credible in this context, at least  
400 three independent experts in the relevant field should be consulted. Each expert should  
401 estimate the incidence of the disease or condition or, if the device is a diagnostic, the  
402 number of patients that would be subjected to diagnosis per year by the device in the  
403 United States. An explanation of the basis for each of the expert’s computations should  
404 also be included. Regardless of the total number of experts consulted, the findings of  
405 each expert should be provided, whether supportive, non-supportive, or inconclusive.

406  
407 Simply stating that the incidence of the disease is fewer than 4,000 patients per year in  
408 the United States or that fewer than 4,000 patients per year in the United States would be  
409 subjected to diagnosis by the device is not adequate for HUD designation. Inappropriate  
410 documentation or insufficient evidence of the incidence determination may result in  
411 disapproval of the HUD request. 21 CFR 814.102(b)(3)(i).

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413 **IV. SPECIAL CONSIDERATIONS**

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415 **A. Pediatrics**

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417 For the purpose of HUD designation requests, the pediatric population is defined as those  
418 younger than 22.0 years of age (i.e., inclusive of the patient’s 21st year of life). Section  
419 520(m)(6)(E)(i) of the FDCA and FDA Guidance on *Premarket Assessment of Pediatric*  
420 *Medical Devices* (May 2004). A device may be eligible for HUD designation in the  
421 pediatric population if the pediatric population affected by the disease or condition in  
422 question is fewer than 4,000 in the United States per year.

423  
424 Devices approved under HDE by CDRH or CBER for a pediatric population or a  
425 pediatric subpopulation on or after September 27, 2007 may be eligible to be sold for  
426 profit, subject to the limitations in section 520(m) of the FD&C Act and described in the  
427 FDA Guidance, *Humanitarian Device Exemption (HDE) Regulation: Questions and*  
428 *Answers* (July 2010).<sup>10</sup>

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<sup>10</sup> This guidance is available at [www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm110194.htm](http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm110194.htm). As explained in this guidance, section 520(m) of the FD&C Act authorizes certain 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 an upper limit known as the “Annual Distribution Number,” or ADN.