Draft Guidance for Industry and Food and Drug Administration Staff

Humanitarian Use Device (HUD) Designations

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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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

I. INTRODUCTION

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

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

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

[1] This guidance is available at www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm110194.htm.

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

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

II. BACKGROUND

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

Devices that receive HUD designation may be eligible for marketing approval under an HDE application. An HDE application is a premarketing application that is similar to a premarket approval (PMA) application in that the applicant must demonstrate a reasonable assurance of safety, but in an HDE application the applicant seeks an exemption from the PMA requirement to demonstrate a reasonable assurance of effectiveness. A device that has received HUD designation is eligible for HDE approval if, among other criteria, the probable benefit to health from use of the device 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. Section 520(m) of the FD&C Act; 21 CFR 814.104(b)(2).[2] FDA approval of an HDE application authorizes the applicant to market the device. This marketing is subject to certain profit and use restrictions set forth in section 520(m) of the FD&C Act. For more information on HDE applications and profit and use restrictions, see the FDA Guidance on *Humanitarian Device Exemption (HDE) Regulation: Questions and Answers* (July 2010).[3]

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

[2] 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).

[3] This guidance is available at www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm110194.htm.

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

Office of Orphan Products Development
Food and Drug Administration
10903 New Hampshire Avenue
WO32-5271
Silver Spring, MD 20993

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

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

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

III. CONTENTS OF HUD DESIGNATION REQUESTS

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

(1) A statement that the applicant requests HUD designation for a rare disease or condition or a specifically identified valid subset of a common disease or condition (see Section III.C).

(2) The title, name, address, and telephone number of the applicant and the primary contact person(s). An email address for the primary contact person(s) is recommended.

(3) A description of the rare disease or condition for which the device is to be used, ideally with particular emphasis on the specific aspects of the disease or condition relevant to the

[4] We encourage applicants to submit a copy of the designation letter with their HDE application, rather than just a reference to this letter.

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

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

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

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

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

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

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

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

A. Description of the Disease or Condition

[5] See, for example, 21 CFR 809.3(a) (definition of *in vitro* diagnostic products).

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

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

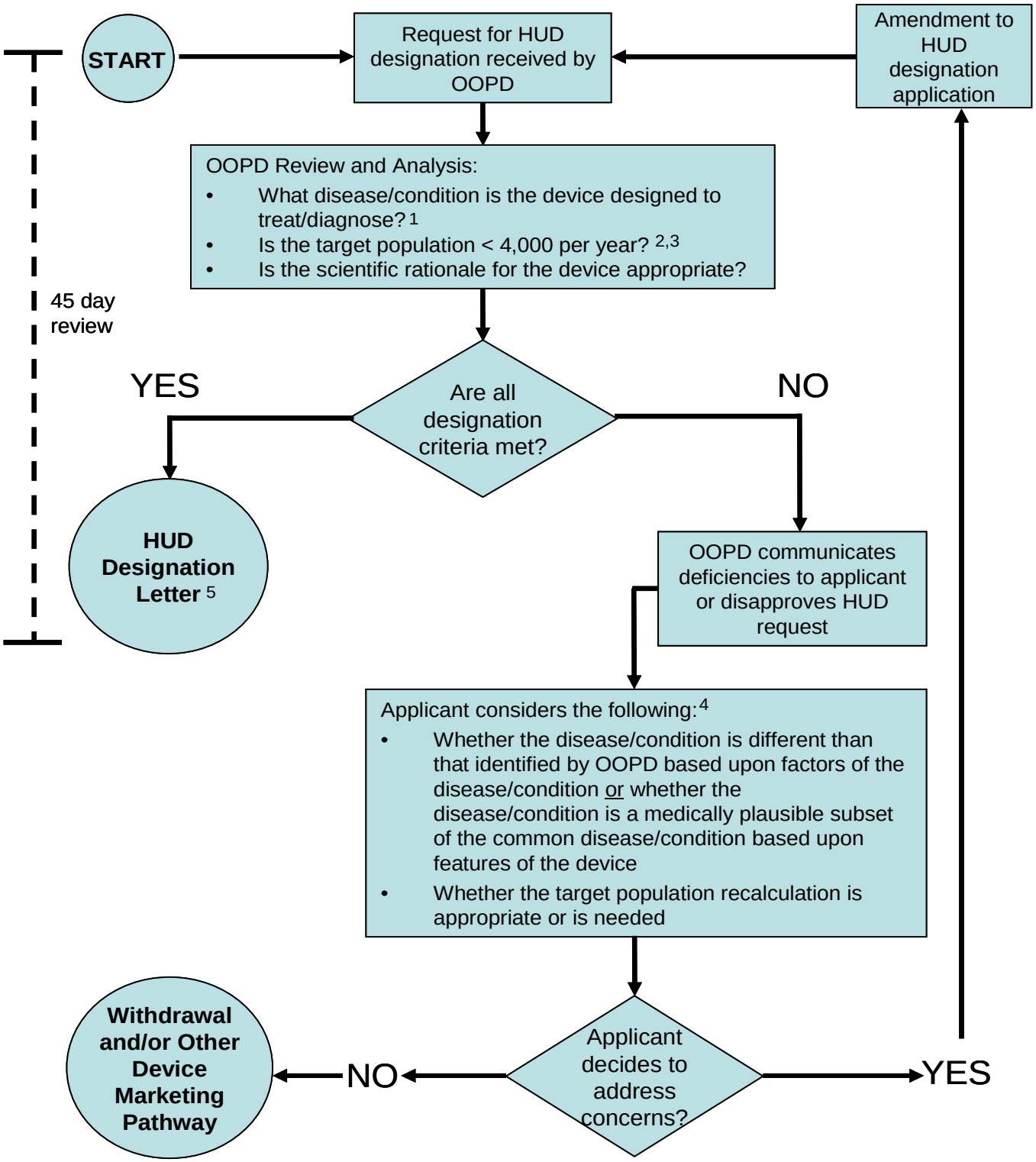
The OOPD independently evaluates the disease or condition that the device is designed to treat or diagnose. Based on this independent evaluation, the OOPD may determine that the disease or condition that the device is designed to treat or diagnose is broader than, or different from, that proposed by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

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

See also "Simplified HUD Decision Flowchart," below, that describes the OOPD review process for a HUD designation request.[6]

[6] 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.

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 then 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.[7]

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[8] – 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),

[7] 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.

[8] 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.

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

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

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

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

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

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

B.3 Devices Intended For Repeat or Multiple Use

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

subjected to diagnosis by the device in a given year – not on the total number of devices expected to be used in a given year.[9]

C. Medically Plausible Subset

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."

"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.

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.

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.

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:

- 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

[9] See 21 CFR 814.126(b)(1)(iii).

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

- Proposed restrictive labeling for the device absent medical or scientific justification for that restriction. For example, restricting the indication to a subset of patients with a particular pathohistologic grade or clinical stage of a specific malignancy does not render the subset "medically plausible" absent some reason to believe the device cannot be used to treat all remaining patients with the malignancy regardless of disease grade or stage.
- Patients who meet or do not meet the inclusion or exclusion criteria of a given clinical trial, absent further justification.
- Patients with an unmet medical need, without further justification.
- The current "standard of care" may not represent a medical plausible subset because the standard of care evolves over time and the device may be appropriate to be used in the larger target population.

In general, the OOPD designates a device for 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. This is true even if the applicant may ultimately pursue marketing approval of the device for an even narrower indication.

D. Device Description and Scientific Rationale for its Proposed Use

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

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

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

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

IV. SPECIAL CONSIDERATIONS

A. Pediatrics

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

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

[10] This guidance is available at 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.