The 21st Century Cures Act (Cures), signed into law on December 13, 2016, amended several sections of the Federal Food, Drug, and Cosmetic Act. This guidance was developed and issued prior to the enactment of Cures, and certain sections of this guidance may no longer be current as a result. FDA is assessing how to revise this guidance to represent our current thinking on this topic. For more information please contact orphan@fda.hhs.gov.

Guidance for Industry and Food and Drug Administration Staff

Humanitarian Use Device (HUD) Designations

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Written comments and suggestions may be submitted at any time for Agency consideration to the Division of Dockets Management, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD, 20852. Alternatively, electronic comments may be submitted to http://www.regulations.gov. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*. Comments may not be acted upon by the Agency until the document is next revised or updated.

For questions regarding this document contact Mr. Eric Chen at 301-796-6327 or 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)

Guidance for Industry and Food and Drug Administration Staff

Humanitarian Use Device (HUD) Designations

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Contains Nonbinding Recommendations

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Guidance for Industry and Food and Drug Administration Staff

Humanitarian Use Device (HUD) Designations

This guidance represents 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's (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 ("HUD requests" or "requests"). Topics addressed in this guidance include:

- 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;
- how this demonstration varies depending on whether the device is intended for therapeutic or diagnostic purposes;
- how properties of the device may affect this demonstration; and
- for the purpose of a HUD request, identifying a medically plausible subset ("orphan subset") of persons with a given disease or condition that affects or is manifested in 4,000 individuals or more in the United States per year.

This guidance addresses only HUD requests, which 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.*[1]

This guidance is responsive to the congressional mandate in section 740 of the fiscal year 2010 U.S. Appropriations Act (Agriculture, Rural Development, Food and Drug Administration, and Related Agencies Appropriations Act, 2010, Public Law 111-80) dated October 21, 2009. Among other things, the congressional mandate required that the Commissioner of Food and Drugs establish a review group within FDA to describe its findings and make recommendations on issues related to rare and neglected diseases and, in part, to develop guidance document(s) based upon these recommendations.

Certain FDA guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, these 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

HUD designations are requirements of the HDE provisions in the Safe Medical Devices Act (SMDA) of 1990 (Public Law 101-629), as amended.[2] See section 520(m) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 USC § 360j(m). 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."[3]

Devices that receive HUD designation may be eligible for marketing approval under an HDE application. An HDE application is a marketing 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 of demonstrating a reasonable assurance of effectiveness. A device that has received HUD designation is eligible for HDE approval if, among other criteria, the device will not expose patients to an unreasonable or significant risk of illness or injury and 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)(2)(C) of the FD&C Act, 21 USC § 360j(m)(2)(C); 21 CFR

[1] The July 2010 version of this guidance is available at www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm110194.htm. This version reflects legislative changes made to the HDE provision as part of the FDA Amendments Act (FDAAA) of 2007; it does not reflect more recent changes enacted as part of the Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012. Until this guidance is updated, you may contact the persons identified on the title page of the July 2010 version for questions related to the FDASIA changes.

[2] The HDE provisions have been amended several times since 1990, in the FDA Modernization Act (FDAMA) of 1997, in FDAAA of 2007, and in FDASIA of 2012.

[3] If there are questions about whether your product is subject to regulation as a medical device, you should contact the Office of Combination Products (OCP) by e-mail at combination@fda.gov or by phone at 301-796-8930.

814.104(b)(2).[4] FDA approval of an HDE application authorizes the applicant to market the device. This marketing approval is subject to certain profit and use restrictions set forth in section 520(m) of the FD&C Act, 21 USC § 360j(m).

Although a HUD designation from 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.

The required contents of a HUD request are set forth in 21 CFR 814.102, and described in detail in Section III of this guidance document. Once a HUD 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
WO32-5271
10903 New Hampshire Avenue
Silver Spring, MD 20993

Section 745A of the FD&C Act requires applicants to include an electronic copy of certain submission types, including presubmissions and submissions under section 520(m) of the FD&C Act, 21 USC § 360j(m), after issuance of final guidance implementing that provision. FDA has issued *Draft Guidance for Industry and FDA Staff: eCopy Program for Medical Devices*.[5] Upon finalization of the eCopy guidance, applicants will be required to include an eCopy as one of the two required copies of their HUD request.

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

If OOPD approves the HUD request, 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 OOPD's HUD designation letter for the device. 21 CFR 814.104(b)(1).[6]

[4] Additionally, to be eligible for HDE approval, the applicant must certify that no comparable device, other than another device approved under the HDE provision or a device approved under an Investigational Device Exemption, 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 USC § 360j(m); 21 CFR 814.104(b)(2).

[5] This draft guidance dated October 17, 2012 is available at http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM313794.pdf

[6] We encourage applicants to submit an actual copy of the designation letter with their HDE application.

If questions arise regarding HUD requests or the program in general, OOPD may be contacted at orphan@fda.hhs.gov or 301-796-8660.

III. CONTENTS OF HUD REQUESTS

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

(1) A statement that the applicant requests HUD designation for a rare disease or condition or a specifically identified orphan subset of a non-rare disease or condition. For the purpose of HUD requests, a "rare disease or condition" is one that affects or is manifested in fewer than 4,000 individuals in the United States per year; a "non-rare disease or condition" is one that affects or is manifested in 4,000 or more individuals in the United States per year. [7] For further explanation of population estimates in HUD requests, and specifically how these estimates vary depending on whether the device is intended for therapeutic or diagnostic purposes, see Section III.B below.

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

(3) A description of the rare disease or condition that the device treats or diagnoses, ideally with particular emphasis on the specific aspects of the disease or condition relevant to the functionality of the device, as well as the proposed indication(s) for use of the device[8] and the reasons why such therapy is needed.

- If the device treats or diagnoses a non-rare disease or condition, then the applicant must demonstrate an orphan subset for the device (see Section III.C). [9]

(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 or an orphan subset of a non-rare disease or condition (see Section III.D).

(5) Documentation, with appended authoritative references, to demonstrate that the device is designed to treat or diagnose a rare 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). Similar documentation is required to demonstrate that fewer than 4,000 people in the

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[7] See section 520(m)(2)(A) of the FD&C Act, 21 USC 360j(m)(2)(A); 21 CFR 814.102(a)(5).

[8] As described elsewhere in this guidance, OOPD designates a device for use in a rare disease or condition or in an orphan subset of a non-rare disease or condition, not for particular indication(s) for use or proposed labeling. The proposed indication(s) for use of the device are nonetheless relevant to a HUD request to help OOPD assess what disease or condition the device treats or diagnoses.

[9] FDA uses the same terminology, "orphan subset," when evaluating requests for HUD and orphan-drug designations. It is important to note, however, that Congress created different eligibility criteria for HUD designations than for orphan-drug designations. For HUD designations, one eligibility criterion is that the disease or condition in question affects *fewer than 4,000 individuals* in the United States ("rare disease or condition" for the purpose of HUD requests), whereas for orphan-drug designations one such criterion is that the disease or condition affects *fewer than 200,000 individuals* in the United States ("rare disease or condition" for the purpose of orphan-drug designation requests). FDA nonetheless employs the same terminology, "orphan subset," for HUD designations as for orphan-drug designations because the limiting principle is the same: some property or properties of the device or drug preclude its use outside of an "orphan subset" of a non-rare disease or condition (e.g., adverse event profile of the product, mechanism of action of the product, etc.). For more on orphan subsets in HUD requests, see Section III.C of this guidance.

United States per year make up a valid orphan subset for a non-rare disease or condition (see Section III.C).

- If the device is intended for diagnostic purposes,[10] 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. See 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 requests containing a statement that requests either HUD designation for a rare disease or condition, or a specifically identified orphan subset of a non-rare 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 e-mail address of the applicant and primary contact person(s);
- adequate description of the rare disease or condition or documentation of an orphan subset of a non-rare disease or condition;
- proposed indication(s) for use of the device;
- adequate description of the device and the scientific rationale for its use as proposed;
- population estimate;
- bibliography;
- copies of all cited references separated by tabs; and
- appendices, if applicable.

Below, we provide clarity on particular elements of HUD requests that have historically caused confusion among applicants. In particular, we focus on the disease or condition that the device treats or diagnoses, population estimates, orphan subsets, device descriptions, scientific rationales, and supporting documentation.

A. Description of the Disease or Condition

A HUD request must include a description of the rare disease or condition that the device treats or diagnoses, or the non-rare disease or condition in the case of an orphan subset. 21 CFR 814.102(a)(3). As noted above, a "rare disease or condition" for the purpose of HUD requests is one that affects or is manifested in fewer than 4,000 individuals in the United States per year.[11] 21 CFR 814.102(a)(5). Ideally, the description of the rare disease or condition 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.

[10] See, for example, 21 CFR 809.3(a) (definition of *in vitro* diagnostic products).
[11] See *supra* note 9.

OOPD designates a device for a rare disease or condition (or for an orphan subset of a non-rare disease or condition, as described in Section III.C), not for a specific indication or proposed labeling for the device.[12] In general, when OOPD gives a HUD designation to a device for a rare disease or condition (or orphan subset), it will designate the device for use by all persons with that rare disease or condition (or orphan subset), even if the applicant may eventually obtain HDE marketing approval for only select indications within that rare disease or condition (or orphan subset). That is, whatever the scope of HUD designation, the scope of marketing approval is governed by the data and information submitted in the marketing application for the device. It is therefore not uncommon for the HUD designation to be broader than the indication(s) for which the device is eventually approved via HDE. For example, at the HUD stage, a device may be designated for treatment of fetal bladder obstruction regardless of gestational age, but at the HDE stage, the device may be approved for treatment of fetal bladder obstruction only in fetuses of 18 to 32 weeks gestational age, based on the data and information submitted in the HDE marketing application.

When reviewing HUD requests, OOPD first asks what disease or condition the device treats or diagnoses. Assume, for example, that an applicant states in a HUD request that a device treats multiple myeloma. Upon reviewing the HUD request, OOPD will consider how the device works to treat or diagnose the disease or condition. OOPD may determine that the device does not in fact treat multiple myeloma, but instead treats a manifestation of multiple myeloma, where the device, for example, is intended to fill lytic lesions in patients with multiple myeloma, but does not treat the multiple myeloma itself.

In this example, for designation purposes, OOPD may initially consider the disease or condition that the device treats or diagnoses to be the lytic lesions and not the multiple myeloma. OOPD may then ask the sponsor for additional information to determine whether lytic lesions due to multiple myeloma should be considered a distinct "disease or condition" from lytic lesions due to other causes (e.g., bone metastasis or hemangioma). Showing that a disease or condition is distinct for designation purposes generally entails a cumulative assessment of a number of factors, including: pathogenesis of the disease or condition; course of the disease or condition; prognosis of the disease or condition; and resistance to treatment. Absent information justifying that lytic lesions from multiple myeloma should be considered a different condition than lytic lesions from other causes, OOPD may consider the disease or condition treated by this device to be lytic lesions regardless of cause and the sponsor may be asked to provide a population estimate that includes patients with lytic lesions from all causes.

Identifying the appropriate disease or condition that the device treats or diagnoses (e.g., multiple myeloma, lytic lesions regardless of cause, or lytic lesions due to multiple myeloma) is critical to estimating the affected patient population, as described below.

[12] See *supra* note 8.

B. Population Estimates

In seeking HUD designation, it is important to understand the difference between disease prevalence and disease incidence. 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 per year") in an attempt to clarify that it interprets the statutory provision as annual incidence, not as point prevalence.[13]

The method for estimating the affected population in HUD requests varies depending on whether the device is intended for therapeutic or diagnostic purposes. For *therapeutic devices*, as described below, 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*, as described below, the population estimate is generally the number of patients per year who would be subjected to diagnosis with the device, regardless of whether the test result is positive or negative. Because of this difference, each applicant should identify in a HUD request whether the device is intended for therapeutic or diagnostic purposes.

B.1 Therapeutic Devices – The Number of New Patients Per Year Who Are Diagnosed with the Disease or Condition and Who Would be Eligible for Treatment with the Device

Therapeutic devices are eligible for HUD designation if they treat a disease or condition with an annual incidence of fewer than 4,000 individuals in the United States. Annual incidence in this context generally means the number of new patients per year who are diagnosed with the disease or condition and who would be eligible for treatment with the device, given the characteristics of the disease or condition and the properties of the device.

Below are three examples of annual incidence estimates for therapeutic devices that exemplify the ways in which incidence is impacted by differences in the characteristics of the device and of the disease or condition in question:

- **Sample Incidence Estimate for HUD Request Involving All New Patients Diagnosed with a Disease or Condition:** Assume a HUD request is submitted for a device designed to treat patients with cystic fibrosis by reducing respiratory complications. The incidence estimate for this request would generally include all new patients diagnosed with cystic fibrosis per year.

[13] 61 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, 21 USC 360j(m), 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. *Id.* 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. *Id.*

- **Sample Incidence Estimate for HUD Request to Reduce Flare-ups of a Disease or Condition:** Assume a HUD request is submitted for a device designed to treat patients with multiple sclerosis (MS) by reducing MS flare-ups. The incidence estimate for this request would generally include all new patients diagnosed with MS per year, no matter how many flare-ups each patient with MS may have in a given year.

- **Sample Incidence Estimate for HUD Request of a Disease or Condition Where the Manifestation Treated by the Device May Develop After Initial Disease Diagnosis:** Assume a HUD request is submitted for a device designed to treat respiratory failure in patients with amyotrophic lateral sclerosis (ALS). If OOPD determines respiratory failure in ALS to be different than respiratory failure in other diseases, then the incidence estimate for this request would generally include those patients with ALS who develop respiratory failure in a given year no matter when they were first diagnosed with ALS.

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 estimate 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.

The number of patients per year who would be subjected to diagnosis with the device depends on the disease or condition that the device diagnoses and the circumstances of use. The number of patients would differ, for example, depending on whether the diagnostic is (1) an *initial diagnostic or screening test* used to diagnose or screen a population, (2) a *confirmatory test* used to confirm the diagnosis of individuals who have already screened positive for the disease or condition, (3) a *treatment guide* used to help select or exclude a given therapy for patients with a given disease or condition, or (4) *a monitoring test* used to monitor progression of a given disease or condition.

Below are examples of population estimates for various diagnostic devices:

- An example of a diagnostic device that may qualify for HUD designation is a device that identifies a specific gene rearrangement in patients with a rare malignancy. If the annual incidence of the rare malignancy is fewer than 4,000 new cases per year, then fewer than 4,000 patients per year would be subjected to diagnosis with the device. The device may therefore be eligible for HUD designation.

- An example of a diagnostic device that may qualify for HUD designation is a device that monitors a particular blood chemistry or hematology parameter which is indicative of disease activity. In order to qualify for HUD designation, the number of patients subjected to the device must be fewer than 4,000 patients per

year (i.e., all new patients diagnosed with the disease or condition as well as existing patients with the disease or condition surviving from previous years).

- 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 fewer than 4,000 patients in the United States per year, the diagnostic device would not be eligible for HUD designation because the number of newborn babies subjected to the screening test would exceed the under 4,000 patient per year limit.

- An example of a diagnostic device that may not qualify for HUD designation is a device used to screen patients who exhibit certain symptoms associated with a rare disease or condition, if the same symptoms are also associated with a non-rare disease or condition. The number of patients screened per year would include all patients who exhibit those symptoms; if that number exceeds the under 4,000 patient per year limit, then the diagnostic device would not 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. Devices intended for repeat or multiple use may include a device implanted in more than one organ, multiple devices implanted in a single organ, or a diagnostic used on the same patient on a regular basis (e.g., as a monitoring test). HUD designations for therapeutic devices depend on the total number of new patients with the disease or condition who would be eligible for use of the device in a given year, not on the total number of devices expected to be used in a given year. Thus, for example, if there are 3,000 individuals with a given disease or condition who would each use (on average) a given device four times per year, that device may still be eligible for HUD designation. Likewise, HUD designations for diagnostic devices depend on the total number of new 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.[14]

C. Orphan Subset of a Non-Rare Disease or Condition

If a device is designed to treat or diagnose a non-rare disease or condition, it is eligible for HUD designation only if the sponsor can show that the device is in fact designed to treat or diagnose an "orphan subset" of this population that occurs in fewer than 4,000 people in the United States per year. See 21 CFR 814.102(a)(3).

"Orphan subset" is a regulatory phrase used to describe the subset of individuals with a non-rare disease or condition on whom use of a device is appropriate, where use of the device on the remaining individuals with that disease or condition would be inappropriate given some intrinsic feature of the device (e.g., adverse event profile or mode of

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

action).[15] An orphan subset cannot be considered without reference to the device, specifically to the property or properties of the device that render it medically or scientifically inappropriate to use outside of the subset of interest in the remaining persons with the non-rare disease or condition. Factors that may inform whether an appropriate orphan subset exists for this purpose include the following inherent properties of a device:

- **Mechanism of Action of the Device:** The mechanism of action of a device may render it scientifically or medically appropriate to limit use of the device to only a subset of patients with a non-rare disease or condition. It may be reasonable to expect that certain targeted therapies would be used in only a subset of patients based on device functionality. For example, it may be appropriate to limit use of a rigid stent to treatment of only certain locations in the brain in a disease that is otherwise non-rare, because in other locations of the brain, the tortuosity of the vessels may prevent adequate deployment of the stent.

- **Adverse Event Profile:** The adverse event profile of a device for a non-rare disease or condition may mean that the device should not be used to treat all persons with the disease or condition who can be treated with other, less risky therapies. Consider, for example, an implantable device that treats a non-rare disease or condition and is known to have a serious adverse event profile because of the risks associated with the implantation process. It may be possible to establish an orphan subset for this device by showing that it would be medically or scientifically appropriate, based on the adverse event profile, to restrict use of the device to only those patients who are refractory to drug therapy. The serious adverse event profile may preclude use of the device in patients who have not failed drug therapy, when therapies with fewer risks are available to these patients.

- **Other Clinical Experience with the Device:** Information on the device's activity, available from completed clinical trials or published in clinical literature may be used to establish an orphan subset. For example, if relevant data show that the device has no significant activity in the subset of patients with high grade tumors but there is some reason to expect that it might have activity in patients with low grade tumors, then patients with low grade tumors may constitute an orphan subset within a given disease or condition.

It is important to understand that an orphan subset does **not** simply mean any medically recognizable or clinically distinguishable subset of persons with a non-rare disease or condition. For a HUD designation, device property(ies) must preclude its use in the remaining persons with the non-rare disease or condition. HUD designation facilitates the pathway to market for devices truly designed for small populations by making those devices eligible for exemption from the PMA effectiveness requirement, as described above in Section II. Accepting limitations of this sort, without further justification (*i.e.*, reference to feature(s) of the device

[15] See *supra* note 9.

that render use outside of the subset of interest scientifically or medically inappropriate), would allow for artificially narrow subsets for the purpose of HUD designation and would be inconsistent with the purpose of the HDE provision. Factors that do **not** inform whether an orphan subset exists include, for example:

- **Clinical Trial Eligibility:** An orphan subset would not be appropriate where the subset of interest is defined only by eligibility to enroll in a given clinical trial to support a specific indication for use of a device, and where there is no scientific or medical reason to preclude use of the device in the remaining persons with the same non-rare disease or condition. Similarly, patients who do not meet inclusion or exclusion criteria for a trial do not automatically qualify as an orphan subset because it could be medically appropriate to evaluate the same device for use in the remaining persons with the non-rare disease or condition, outside of the subset of interest.

- **Sponsor's Plan to Study the Device for a Select Indication:** An orphan subset does not exist simply because the sponsor plans to study the device for only a select indication within a non-rare disease or condition, absent a plausible argument why the device could not be used to safely or effectively treat the remaining persons with the non-rare disease or condition.

- **Unmet Medical Need:** Patients with a non-rare disease or condition who have an unmet medical need do not automatically constitute an orphan subset unless the applicant can justify limiting use of the device to only that subset, based on limiting feature(s) of the device, as described above.
- **Current "Standard of Care":** Opinions regarding the current "standard of care" as it relates to the use of a device on certain individuals cannot be the basis for identifying an orphan subset. The standard of care will evolve with study of the new treatment option and it may be determined, at some point, that it is medically or scientifically appropriate to use the device in a larger population with the non-rare disease or condition.
- **Price:** An orphan subset of a non-rare disease or condition does not exist because of price considerations. The applicant would instead need to justify limiting use of the device to the subset of interest based on feature(s) of the device that preclude its use in the broader population with the same non-rare disease or condition.

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,

photographs, or other visual representations 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 orphan subset of a non-rare disease or condition (see Section III.C) in the HUD request should contain all relevant preclinical, clinical, and/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 device design specifications is reviewed in the HDE marketing application and not in the HUD 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 therapeutic devices, this documentation must demonstrate that the annual incidence of the disease or condition is fewer than 4,000 patients per year. 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. See Sections III.B.1 and III.B.2 for population estimates and 21 CFR 814.102(a)(5). Authoritative references in this context include "literature citations in specialized medical journals, textbooks, specialized medical society proceedings, or governmental statistics publications." 21 CFR 814.102(a)(5).

We recommend including in HUD requests all relevant documentation on the population estimate – whether supportive, non-supportive, or inconclusive. If literature and other resources are inadequate 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, with methodology, 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 provide his/her estimate, and methods used to reach this estimate, of the annual incidence of the disease or condition that the device treats 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. See Sections III.B.1 and III.B.2 for population estimates. 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. Insufficient evidence of the population estimate may result in disapproval of the HUD request. 21 CFR 814.102(b)(3)(i).

IV. PEDIATRIC CONSIDERATIONS

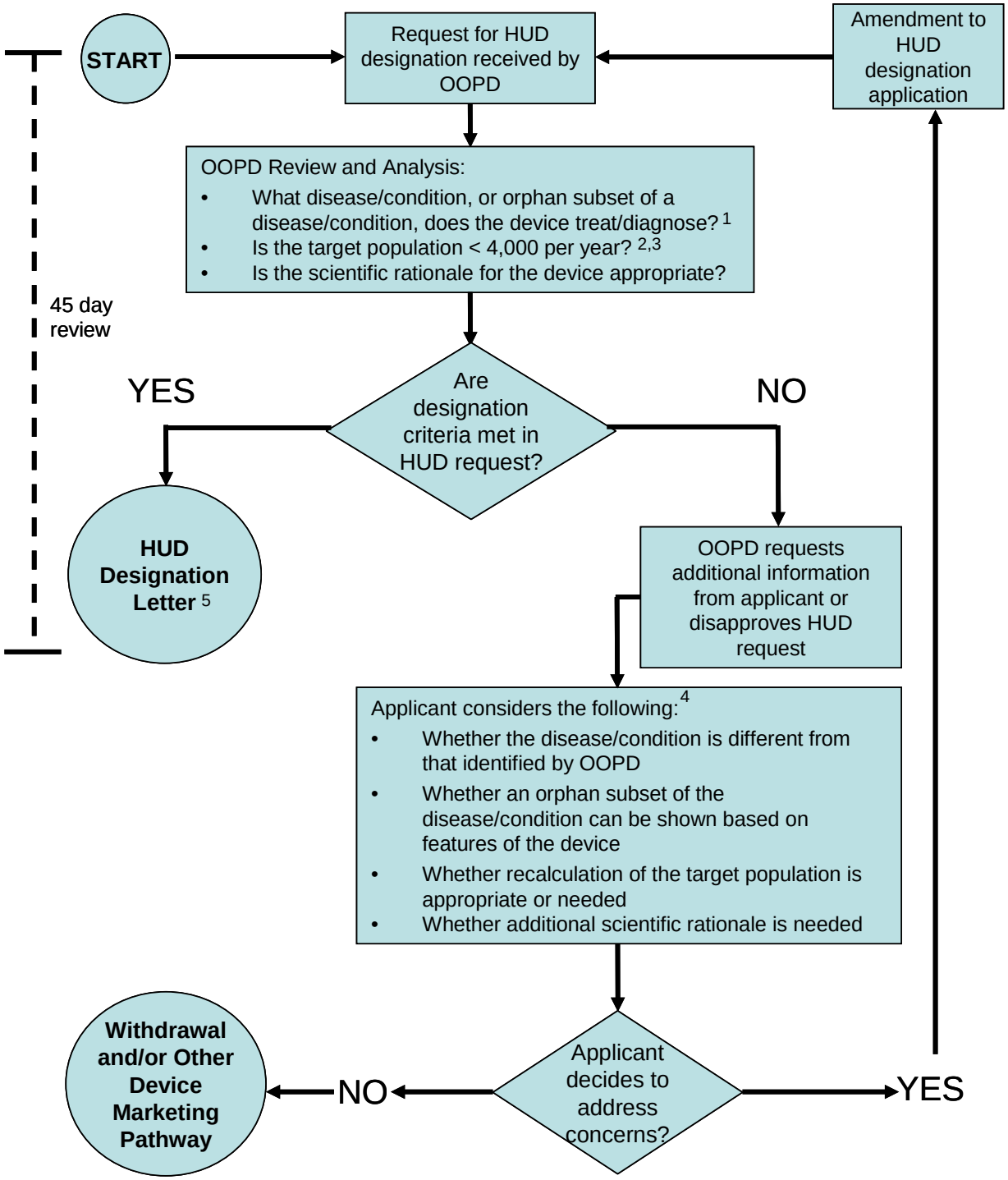
For the purpose of HUD requests, the pediatric population is defined as those younger than 22 years of age (i.e., inclusive of the patient's 21st year of life). See section 520(m)(6)(E)(i) of the FD&C Act, 21 USC 360j(m)(6)(E)(i) and FDA Guidance on *Premarket Assessment of Pediatric Medical Devices*.[16] Generally, OOPD will designate for the entire population (i.e., pediatric and adult) if the incidence of the disease or condition affects or is manifested in fewer than 4,000 patients per year in the United States. However, in situations where the entire population is greater than or equal to 4,000 patients per year, 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.

V. HUD DECISION FLOWCHART

The "HUD Decision Flowchart" serves as a quick guide and outlines the OOPD review process for a HUD request but does not include other issues or considerations that may arise during a HUD request review and are otherwise discussed in this guidance document. This guide shows that in its review, OOPD identifies the disease or condition that the device treats or diagnoses, evaluates the population estimate, and reviews the scientific rationale for the device. OOPD has 45 days to review the submission and provide official communication to the applicant.

[16] This guidance is available at http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089742.pdf.

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 who 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 with OOPD regarding concerns
5. Applicant may submit HDE marketing application after receiving the HUD designation letter