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Draft – Not for Implementation

Humanitarian Device Exemption (HDE) Program

Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

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For questions about this document regarding CDRH-regulated devices, contact HDE Staff, Center for Devices and Radiological Health, at 301-796-5640. For questions about this document regarding CBER-regulated devices, contact the Office of Communication, Outreach, and Development (OCOD) at 1-800-835-4709 or 240-402-8010.

When final, this guidance will supersede "Guidance for HDE holders, Institutional Review Boards (IRBs), Clinical Investigators, and Food and Drug Administration Staff, Humanitarian Device Exemptions (HDE) Regulation: Questions and Answers," issued July 8, 2010.

U.S. FOOD & DRUG ADMINISTRATION

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Center for Biologics Evaluation and Research
Office of Orphan Products Development

Preface

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Humanitarian Device Exemption (HDE) Program

Draft Guidance for Industry and Food and Drug Administration Staff

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff or Office responsible for this guidance as listed on the title page.

I. Introduction

FDA developed this draft guidance document to provide clarity to industry and FDA staff about the current review practices for the Humanitarian Device Exemption (HDE) Program. This programmatic draft guidance addresses commonly asked questions about HDEs and Humanitarian Use Devices (HUDs), including FDA actions on HDE applications, post-approval requirements, and special considerations for devices marketed under the HDE Program. This draft guidance document reflects changes in the HDE Program resulting from statutory amendments made by the 21st Century Cures Act (Cures Act)[1] and explains the criteria FDA considers to determine if "probable benefit" has been demonstrated as part of the Agency's decision-making process regarding marketing authorization for a HUD. This draft guidance document also reflects amendments made to the HDE provision of the Federal Food, Drug, and Cosmetic Act (FD&C Act) by the FDA Reauthorization Act of 2017 (FDARA).[2] Once finalized, this guidance will supersede "Guidance for HDE holders, Institutional Review Boards (IRBs), Clinical Investigators, and Food and Drug Administration Staff, Humanitarian Device Exemptions (HDE) Regulation: Questions and Answers," issued July 8, 2010.

For the purposes of this guidance, "you" refers to the HDE applicant or holder, and "we" refers to FDA. FDA's guidance documents, including this draft 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

[1] Pub. L. 114-255.
[2] Pub. L. 115-52.

requirements are cited. The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

II. Background

HUDs are medical devices intended to benefit patients in the treatment or diagnosis of diseases or conditions that affect or are manifested in not more than 8,000 individuals in the United States per year.[3] In seeking marketing authorization under an HDE application, the first step is the preparation and submission of a HUD designation request to FDA's Office of Orphan Products Development (OOPD). For more information on this step of the process, see the FDA guidance "Humanitarian Use Device (HUD) Designations."[4] We will refer to that document as the "HUD Designations Guidance" for the purposes of this draft guidance. The HDE application, which is the primary focus of this guidance document, is the second step in seeking marketing authorization for a HUD.

To the extent consistent with the protection of the public health and safety and with ethical standards, the purpose of the HDE provision is to "encourage the discovery and use of devices intended to benefit patients in the treatment and diagnosis of diseases or conditions that affect not more than 8,000 individuals in the United States,"[5]

FDA may grant an HDE, which is an exemption from the effectiveness requirements of sections 514 and 515 of the FD&C Act, if we find that the device meets all of the following criteria:

1. 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 while taking into account the probable risks and benefits of currently available devices or alternative forms of treatment;
2. The device would not be available to a person with the disease or condition in question without the HDE, and no comparable device, other than another device approved under an HDE or Investigational Device Exemption (IDE)[6] is available to treat or diagnose such disease or condition; and
3. The device is designed to treat or diagnose a disease or condition that affects not more than 8,000 individuals in the United States on an annual basis.[7]

[3] 21 CFR 814.3(n). As subsequently explained, the current threshold is "not more than 8,000 individuals in the United States." Before section 3052 of the Cures Act took effect, the threshold was "fewer than 4,000 individuals in the United States."

[4] Available at https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm336515.pdf.

[5] Section 520(m)(1) of the FD&C Act.

[6] An approved IDE permits a device to be shipped lawfully for the purposes of conducting investigations of the device without complying with certain other requirements of the FD&C Act that would apply to devices in commercial distribution. See section 520(g) of the FD&C Act; 21 CFR 812.1(a).

[7] See section 520(m)(2) of the FD&C Act; 21 CFR 814.104(b)(1)-(3).

The HDE provision was added to the FD&C Act by the Safe Medical Devices Act of 1990 and included, among other things, a prohibition on profits from sale of HUDs and a requirement that before "use" of a HUD to treat or diagnose patients at a facility, an IRB must approve such use.[8] For purposes of this draft guidance, approving the "use" of a HUD (as opposed to approving the "investigational use" or a "clinical investigation" of a device) refers to use of the HUD in the course of routine clinical care to treat or diagnose patients. Subsequent amendments to the FD&C Act have added important flexibility to the HDE program while retaining the purpose of encouraging the discovery of medical devices for use in limited patient populations.

The Food and Drug Administration Modernization Act of 1997 (FDAMA) included a section on expanding the humanitarian use of devices,[9] which among other provisions:

- Allowed for the use of HUDs under HDEs without prior IRB approval in certain emergency situations (see Section VIII.G for more information); and
- Provided that FDA may suspend or withdraw an HDE only after providing notice and an opportunity for an informal hearing (see Section VII.E for more information).

The Food and Drug Administration Amendments Act of 2007 (FDAAA) further modified the HDE provision, providing that HUDs indicated for use in pediatric patients, or in a pediatric subpopulation may be sold for profit, subject to certain restrictions.[10] The scope of HDE-approved devices eligible to make a profit was expanded by section 613 of the Food and Drug Administration Safety and Innovation Act (FDASIA).[11] Currently, a HUD is eligible to be sold for profit after receiving HDE approval only if, in addition to meeting other criteria, the number of HUDs sold during any calendar year does not exceed the annual distribution number (ADN), which is the number of devices reasonably needed to treat, diagnose, or cure a population of 8,000 individuals in the United States (see Section VIII.A for more information).

FDAAA also added section 515A to the FD&C Act, which requires, among other things, the inclusion of additional information regarding pediatric uses in all original HDE applications, if such information is readily available.[12] Specifically, section 515A of the FD&C Act requires that each new HDE application include a description, based on readily available information, of any pediatric subpopulations that suffer from the disease or condition that the device is intended to treat, diagnose, or cure, and the number of affected pediatric patients.[13]

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[8] Pub. L. 101-629, section 14.

[9] Pub. L. 105-115, section 203.

[10] Pub. L. 110-85, section 303. Pediatric patients are patients who are younger than 22 years of age at the time of diagnosis or treatment. See section 520(m)(6)(E)(i) of the FD&C Act; 21 CFR 814.3(s).

[11] Pub. L. 112-144. Many of the statutory provisions cited throughout this guidance, including sections 515A(a)(2) and 520(m)(6) of the FD&C Act, were added by section 302 of FDAAA and amended by FDASIA.

[12] See Pub L. 110-85, section 302. For further discussion of the information required for pediatric uses of medical devices under section 515A, see the guidance document, "Providing Information About Pediatric Uses of Medical Devices," (available at https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM339465.pdf).

[13] See section 515A(a)(2) of the FD&C Act.

The Cures Act amended the FD&C Act to increase the maximum number of patients affected by the disease or condition that a HUD is designed to treat or diagnose to "not more than 8,000 individuals in the United States."[14] Further, the Cures Act removed the requirement that institutional review committees, i.e., IRBs, that supervise the clinical testing of devices or approve the use of HUDs be local.[15] See Sections VIII.E and VIII.F below for more information regarding differences between the "use" of a HUD and clinical investigations involving HUDs. The Cures Act also required FDA to publish a draft guidance that defines the criteria for establishing "probable benefit" as that term is used in section 520(m)(2)(C) of the FD&C Act. This draft guidance includes information to define those criteria for HDE applicants, other stakeholders, and FDA staff. See Section III for more information about the scope of this draft guidance.

FDARA further amended section 520(m)(4)(B) of the FD&C Act to allow either an IRB or "an appropriate local committee" to approve the use of a HUD to treat or diagnose patients at a facility.[16] We interpret this provision to provide additional flexibility for a healthcare facility to determine the individuals involved in, and processes and procedures used by, the committee that approves the use of HUDs at that facility in order to meet the needs of patients. Note, however, that this FDARA provision did not change the requirements for IRB oversight of a clinical investigation of a HUD. An "appropriate local committee" may not review and approve such a clinical investigation in place of an IRB.[17]

III. Scope

This draft guidance provides recommendations to industry and FDA staff about the operational aspects of the HDE Program and also explains the principal criteria that FDA considers when determining if probable benefit(s) to health have been demonstrated for a HUD that is being reviewed through the HDE Program. Additionally, this guidance addresses FDA's assessment of whether the probable benefit(s) 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. The decision tools in Appendices B and C are intended to help staff consider the probable benefit-risk factors discussed in Section VI when reviewing HDE applications. This guidance includes sections on the following topics, among others:

- FDA Review Actions for an HDE Application (Section V.B);
- Assessing Probable Benefit and Risk in an HDE Application[18] (Section VI);
- Post-Approval Requirements (Section VII);
- Special Considerations for Devices Marketed Under an HDE (Section VIII); and

[14] Pub. L. 114-255, section 3052.
[15] Pub. L. 114-255, section 3056.
[16] Pub. L. 115-52, section 502(b).
[17] See sections 520(g)(3) and 520(m)(4)(A) of the FD&C Act; 21 CFR part 56; 21 CFR part 812.
[18] As required by the Cures Act, this guidance explains the principal criteria that FDA considers when determining if probable benefit(s) to health have been demonstrated for a HUD that is being reviewed through the HDE Program.

- Appendices to support the HDE Program which include:
  - Filing Checklist (Appendix A)
  - Probable Benefit-Risk Assessment Tools (Appendices B and C)

The overarching principles in this draft guidance are applicable to devices that are eligible for review through an HDE application by CDRH as well as devices that are eligible for review through an HDE application by the Center for Biologics Evaluation and Research (CBER). This guidance is not intended to supplant or provide recommendations regarding device-specific data requirements, but it may cover broader areas not addressed in device-specific guidance documents. In addition, this guidance does not address review issues unique to combination products.

IV. HUD Designations and HDE Applications

Before submitting an HDE application to FDA, an HDE applicant must first prepare and submit a HUD designation request to OOPD and receive a HUD designation.[19] For more information on the preparation and submission of a HUD designation request, refer to 21 CFR 814.102(a) and the HUD Designations Guidance. In the review of a HUD designation request, FDA will determine whether the device is for a rare disease or condition that affects or is manifested in not more than 8,000 individuals in the United States per year. In the case of a device used for diagnostic purposes, FDA will determine whether the documentation demonstrates that not more than 8,000 individuals per year would be subject to diagnosis by the device in the United States.[20] After receiving a HUD designation, the HDE applicant may submit an HDE application to the appropriate center. Each applicant must have its own HUD designation to submit an original HDE application for a proposed indication.[21] Additionally, the HDE applicant can utilize the HDE pathway only if no other comparable device (other than another device approved under an HDE or under an IDE) is available to treat or diagnose the disease or condition.

Note that if your device is part of a combination product, an HDE may not be the appropriate pathway to market. For questions about marketing pathways and regulatory requirements for combination products, please contact the Office of Combination Products by email at combination@fda.gov. For questions about Companion Diagnostic Devices, contact CDRH's Office of In Vitro Diagnostics and Radiological Health at oir-policy@fda.hhs.gov.

V. FDA's Review of HDE Applications

Approval of an HDE application under 21 CFR part 814, Subpart H, is considered "FDA approval" of the device based on, among other criteria, evidence that 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

[19] 21 CFR 814.102(a).
[20] See 21 CFR 814.102(a)(5).
[21] See 21 CFR 814.102(a); 21 CFR 814.104(b)(1)

account the probable risks and benefits of currently available devices or alternative forms of treatment.[22] In addition, to be eligible for HDE application approval, FDA must determine that the device would not be available to a person with the disease or condition in question without the HDE application approval and that there is no comparable device, other than another device under an HDE or IDE, available to treat or diagnose the disease or condition.[23] A HUD that meets the HDE standard for approval is exempt from the requirement of establishing a reasonable assurance of effectiveness that would otherwise be required under sections 514 and 515 of the FD&C Act, but is not exempt from the requirement for a reasonable assurance of safety.[24] FDA approval of an HDE application authorizes an applicant to market a HUD in accordance with approved labeling and indication(s) for use, subject to certain profit and use restrictions set forth in section 520(m) of the FD&C Act.

A HUD under an HDE may not serve as a predicate device for purposes of section 513(i) of the FD&C Act.[25] A Premarket Approval application (PMA) could subsequently be submitted for the same device and indication(s) approved under an HDE application if the applicant believes there is a reasonable assurance of safety and effectiveness; or, if appropriate, the applicant could instead submit a request for classification under section 513(f)(2) of the FD&C Act (a De Novo request). If FDA approves a PMA or grants a De Novo request for the HUD or another comparable device with the same indication, we may withdraw the HDE because the HUD would no longer meet the requirements of section 520(m)(2)(B) of the FD&C Act.[26] Section V.A discusses comparable devices, and Section VII.E discusses HUD designation re-evaluation.

FDA's review of HDE applications has similarities to the review of PMA applications, with a few key differences. Some similarities to the PMA program include:

- HDE amendments, supplements, and reports are generally subject to similar requirements as those for PMAs (although timeframes differ).[27] The requirements for each of these types of HDE submissions refers back to the regulatory requirements for the PMA counterpart.
- HUDs are subject to the quality system (QS) regulation under 21 CFR part 820, and HDE applications must include information in sufficient detail so that FDA can make a knowledgeable judgment about the quality control used in the manufacture of the

[22] Section 520(m)(2)(C) of the FD&C Act; 21 CFR 814.104(b)(3).
[23] Section 520(m)(2)(B) of the FD&C Act; 21 CFR 814.104(b)(2).
[24] See sections 514, 515, and 520(m) of the FD&C Act; 21 CFR 814.118(a)(1). As discussed in more detail in Section VI, FDA will perform an assessment of the probable benefits and risks of a device, considering a number of factors, including the target patient population and the size of the population, as well as available alternative treatments or diagnostics, as part of its determination of whether an HDE application meets the statutory standard for approval.
[25] Under 21 CFR 807.92(a)(3), a legally marketed (predicate) device to which a new device may be compared for a determination regarding substantial equivalence is a device that was legally marketed prior to May 28, 1976 (preamendments device), or a device which has been reclassified from class III to class II or I, or a device which has been found to be substantially equivalent through the 510(k) process.
[26] 21 CFR 814.118(a).
[27] See 21 CFR 814.106 (amendments); 814.108 (supplements); and 814.126 (reports).

device.[28] Additional information on manufacturing information to include in an HDE application can be found in the FDA guidance, "Quality System Information for Certain Premarket Application Reviews."[29] If you believe that you cannot comply with or should not be subject to the QS regulation requirements, you may request an exemption or a variance from any device QS regulation requirement. Petitions for an exemption or variance must be submitted according to the procedures set forth in 21 CFR 10.30.[30]

Key differences between the HDE and PMA programs include the following:

- A HUD under an HDE is *exempt* from the requirement of establishing a reasonable assurance of effectiveness that would otherwise be required under sections 514 and 515 of the FD&C Act.
- HDE applications accepted for filing and to which the applicant does not submit a major amendment are reviewed in 75 days, rather than the traditional 180-day review timeframe for PMA applications.[31]
- HDE applications are not subject to user fees.
- For a device approved under an HDE application, medical device reports (MDRs) submitted to FDA in compliance with the requirements of 21 CFR part 803 shall also be submitted to the IRB of record.[32] If an appropriate local committee, instead of an IRB, approved the use of the device at a facility, FDA recommends that these MDRs be submitted to that committee. See Section VII below for additional information regarding IRB requirements.
- Use of HUDs in the clinical care of patients at a facility requires approval by either an IRB or an appropriate local committee, with the exception of emergency use.[33] See Section VII below for additional information regarding IRB and appropriate local committee requirements.
- An HDE holder can only make a profit, subject to the limit of the ADN, if the device meets the eligibility criteria for the exemption to the profit prohibition in section 520(m)(6)(A)(i), subject to restrictions in section 520(m)(6) of the FD&C Act. See Section VIII.A below for additional information regarding eligibility for profit.
- The applicant must include in the application a statement that no comparable device, other than another HUD approved under an HDE or a device under an approved IDE, is available to treat or diagnose the disease or condition. The applicant must explain in its HDE application why the device would not be available for the indication in question without the HDE approval.[34]

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[28] 21 CFR 814.104(b)(4).
[29] Available at https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070899.pdf.
[30] See 21 CFR 820.1(e).
[31] 21 CFR 814.40 and 814.114.
[32] See 21 CFR 814.126(a).
[33] See section 520(m)(4) of the FD&C Act; 21 CFR 814.124(a).
[34] See section 520(m)(2)(B) of the FD&C Act and 21 CFR 814.104(b)(2).

Applicants wishing to submit a "modular HDE" for their HDE application may use the procedures outlined in the FDA guidance, "Premarket Approval Application Modular Review."[35] A modular HDE, for purposes of this draft guidance, is a compilation of sections or "modules" submitted at different times that together become a complete HDE application. HDE applicants should include a copy of or reference to FDA's HUD designation letter with each HDE modular submission. The modules should conform to the information required for an HDE application.

When submitting an HDE application, applicants must prepare an electronic copy of their submission per the FDA guidance document, "eCopy Program for Medical Device Submissions,"[36] and send the e-copy and cover letter to:

For Products Regulated by CDRH
U.S. Food and Drug Administration
Center for Devices and Radiological Heath
Document Control Center – WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

For Products Regulated by CBER
U.S. Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center – WO71-G112
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

A. HDE Application Required Elements and Filing Review Principles

To use this guidance appropriately, HDE applicants and FDA staff should review the following basic principles that are in bold typeface and followed by a description of FDA's review policies and procedures. These principles, and the objective criteria outlined in the Filing Checklist in Appendix A, inform FDA's HDE application filing decisions.

The contents of the HDE application should allow the substantive review to proceed.

The HDE regulations identify the criteria that, if not met, may serve as the basis for FDA refusing to file an HDE application.[37] The HDE application must contain the basic administrative and scientific elements listed in 21 CFR 814.104(b), unless the applicant justifies an omission in accordance with 21 CFR 814.104(c). The specific questions in the filing checklist are intended to help FDA ensure that the HDE application contents are sufficiently organized and complete to allow the review team to proceed with a substantive review of the application.

[35] Available at https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM089767.pdf.
[36] Available at https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM313794.pdf.
[37] 21 CFR 814.112(a).

The filing decision should not be based on a substantive review of the data and information in the HDE application.

The filing review is conducted to ensure that the HDE application is sufficiently complete and to determine the basic adequacy of the technical elements of the HDE application, respectively. Notably, in determining whether an HDE application should be filed, the submitted information should not be evaluated to determine whether the device will expose patients to an unreasonable risk of illness or injury or whether the probable benefit to health from the 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.

The checklist included in Appendix A is a tool to help ensure that the application contains the necessary information to conduct a substantive review. The elements in the checklist stem from either statutory or regulatory requirements, and the format and content are consistent with the analogous checklists for other types of premarket submissions. FDA generally should not refuse to file an HDE application because we have reviewed the data and believe that the application is ultimately inadequate to meet the standard for HDE approval. Subsequently, the substantive review of the HDE application will evaluate the quality of the content and lead to a decision regarding the safety and probable benefit of the HUD. Concerns identified by the Agency during the filing review regarding results and outcomes of nonclinical and clinical studies would not preclude filing.

FDA should determine whether the applicant provided a justification for any alternative approach.

If the applicant believes any criteria in the checklist are not applicable, the applicant should explain its rationale. Likewise, the applicant should provide a rationale for any deviation from an applicable device-specific or cross-cutting guidance document or FDA-recognized consensus standard. FDA expects that any item in the checklist that is missing from the application will be addressed with a rationale explaining why the item is not applicable and that any deviations will be explained. If a justification to omit certain information or for taking an alternative approach is provided, FDA will consider the adequacy of that justification or alternative approach during substantive review of the application. A given criterion in the checklist will be considered "Not Present" if the application fails to include either the information requested or a rationale for omission.

HDE application filing reviews.

FDA's decision to "File" or "Not File" an HDE application should be made in collaboration with the HDE review team and with the appropriate supervisory oversight. FDA will notify the HDE applicant of the filing status within 30 calendar days from the date the HDE application was received.[38] Generally, a small number of missing items from the filing checklist will not preclude

[38] 21 CFR 814.112(a).

a positive filing decision; however, if multiple items are missing such that a substantive review cannot be completed, a "Not File" decision will typically be made.

Additional considerations when using the filing checklist.

Certain elements of the HDE filing checklist are unique to the HDE Program. These elements are discussed in additional detail below.

Amount charged for the device

As required by 21 CFR 814.104(b)(5), the applicant must state the amount to be charged for the device, and if the amount is more than $250, a report or attestation must be provided verifying that the amount charged does not exceed the costs of the device's research, development, fabrication, and distribution. A report must be prepared by an independent certified public accountant, made in accordance with the Statement on Standards for Attestation established by the American Institute of Certified Public Accountants. In lieu of such a report, an applicant may submit an attestation by a responsible individual of the organization, verifying that the amount charged does not exceed the costs of the device's research, development, fabrication, and distribution. If the amount charged is $250 or less, the requirement for a report by an independent certified public accountant or an attestation by a responsible individual of the organization is waived. Even if an HDE applicant requests that FDA consider whether the HUD meets certain eligibility criteria to qualify for profit making (see Section VIII.A. regarding how to request to make a profit), the applicant must still include this report or attestation in the HDE application.

Comparable Devices

As required by 21 CFR 814.104(b)(2), the applicant must provide a statement that no other comparable device, other than another HUD approved under an HDE or a device under an approved IDE, is available to treat or diagnose the disease or condition. A "comparable device" does not need to be identical to the device that is the subject of the HDE application. However, in applying the "comparable device" exemption criterion, FDA takes into account that the purpose of the HDE Program is to encourage development of devices intended to treat or diagnose diseases or conditions that affect small patient populations. In determining whether a comparable device exists, FDA may consider:

- the device's indications for use and technological characteristics;
- the patient population to be treated or diagnosed with the device; and
- whether the device meets the needs of the identified patient population.

FDA may refuse to file an HDE application if FDA determines that a comparable device is available (other than under another HDE or a device under an IDE) to treat or diagnose such

disease or condition for which the approval of the HDE application is being sought.[39] FDA cannot approve an HDE application for a HUD if we determine that such a comparable device is available.[40]

B. FDA Review Actions for an HDE Application

After an original HDE application or HDE supplement is accepted for filing and FDA begins its substantive review, the Agency may take the following actions during the course of review:[41]

- Approval order;
- Approvable letter;
- Major deficiency letter;
- Not approvable letter; and
- Denial order.

The review timeframe for original HDE applications and HDE supplements is 75 days.[42] In addition, if the applicant submits a major amendment, the review timeframe may be extended up to 75 days.[43] Certain changes to the manufacturing procedure or changes in method of manufacture may qualify to be submitted as a 30-day notice.[44] For more information regarding 30-day notices, refer to the FDA guidance, "30-Day Notices, 135-Day Premarket Approval (PMA) Supplements and 75-Day Humanitarian Device Exemption (HDE) Supplements for Manufacturing Method or Process Changes."[45]

1. Approval Order

FDA will issue an approval order (letter) informing the applicant that the HDE application is approved and that the applicant may begin commercial distribution of the device in accordance with any prescribed conditions of approval after we have completed our review and determined that none of the reasons listed in 21 CFR 814.118 for denying approval applies.[46]

When FDA issues an approval order, the FDA review clock stops. An approval order marks the end of FDA's review, as it is a final action.

[39] See 21 CFR 814.112(a)(2).
[40] See section 520(m)(2)(B) of the FD&C Act.
[41] See 21 CFR 814.106 and 814.116.
[42] See 21 CFR 814.108 and 814.114.
[43] 21 CFR 814.106.
[44] See 21 CFR 814.108 and 814.39(f).
[45] Available at https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM080194.pdf.
[46] See 21 CFR 814.116(b).

2. Approvable Letter

FDA will issue an approvable letter to inform the applicant that we have completed our review of the application and determined that one or both of the following are necessary:[47]

- Resolution of minor deficiencies that are identified in the approvable letter. These deficiencies may include, for example, clarifications of previously submitted information, revisions to the labeling, and revisions to or development of a post-approval study protocol.
- Completion of an FDA inspection that finds the manufacturing facilities, methods, and controls in compliance with the QS regulation, 21 CFR part 820, and, if applicable, verifies records pertinent to the HDE application. When this is the case, the approvable letter states that the device is "approvable pending GMP inspection."

When FDA issues an approvable letter pending resolution of minor deficiencies, we stop the FDA review clock and place the application on hold. When FDA receives a complete response to an approvable letter for an HDE application, we consider it a major amendment and restart the clock with a new 75-day FDA response timeframe.

When FDA issues an approvable letter pending GMP inspection letter, we stop the FDA review clock. Once FDA determines that the GMP issues are resolved, we will issue an approval order if all other minor deficiencies that may have been noted in the approvable letter have also been resolved.

3. Major Deficiency Letter

FDA will issue a major deficiency letter to inform the applicant that the HDE application lacks significant information necessary for FDA to complete our review and request that the applicant amend the application to provide the necessary information regarding the device,[48] such as:

- Additional clinical experience to demonstrate safety and probable benefit;
- Additional non-clinical data to demonstrate safety and probable benefit of the device (e.g., electromagnetic compatibility, electrical safety, biocompatibility, reliability, software, labeling, animal testing[49]);
- Scientific rationale for test data provided in the application;
- New validation data and analyses (e.g., due to device modifications made during the course of the HDE application review); or

[47] See 21 CFR 814.116(c).
[48] See 21 CFR 814.106 and 21 CFR 814.37(b).
[49] We support the principles of the "3Rs," to reduce, refine, and replace animal use in testing when feasible. We encourage sponsors to consult with us if it they wish to use a non-animal testing method they believe is suitable, adequate, validated, and feasible. We will consider if such an alternative method could be assessed for equivalency to an animal test method.

- A re-analysis of previously submitted data (e.g., alternative analytical method).

When FDA issues a major deficiency letter, we stop the FDA review clock and place the application on hold. When FDA receives a complete response to a major deficiency letter, we consider it a major amendment, restart the clock, and review the amendment within 75 days.

4. Not Approvable Letter

FDA will issue a not approvable letter to inform the applicant that we have completed our review and that we do not believe that the application can be approved 'as-is' because of significant deficiencies. The not approvable letter will describe the deficiencies in the application, including each applicable ground for not approving and, where practical, will identify measures required to place the application in an approvable form.[50]

Generally, before FDA issues a not approvable letter, we will first issue a major deficiency letter to provide the applicant with an opportunity to address concerns. However, if an applicant fails to provide an adequate response to a major deficiency letter, or if we have attempted to resolve all deficiencies via interactive review and have not received adequate responses, FDA will issue a not approvable letter.

When FDA issues a not approvable letter, we stop the review clock and place the application on hold. If FDA receives a complete response to a not approvable letter, the amendment will be considered a major amendment, and we restart the clock with a new 75-day FDA response timeframe.[51]

5. Denial Order

FDA may deny approval of an HDE application for any of the reasons identified in 21 CFR 814.118(a). FDA will issue a denial order (letter) when we need to inform the applicant that we have denied approval of the HDE application. The denial order will identify all deficiencies in the application, including each applicable ground for denial and, where practical, will identify measures required to place the application in an approvable form. The denial order will include a notice of an opportunity to request review under section 515(d)(4) of the FD&C Act.[52]

When FDA issues a denial order, we end the FDA review clock if a prior action has not already done so. FDA expects that a denial will normally be preceded by another FDA action that stops the review clock, such as a not approvable letter. However, the FD&C Act does not require any prior FDA action, and FDA may, in appropriate circumstances, proceed directly to issuing a denial order. A denial order marks the end of FDA's review, as it is considered a final action.

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[50] 21 CFR 814.116(d).
[51] See 21 CFR 814.44(f)(1) and 814.116(d).
[52] 21 CFR 814.118(b) and 814.45(b).

6. Acknowledgement of Voluntary Withdrawal

Under FDA regulations for review of HDE applications, FDA considers an original HDE application or HDE supplement to have been voluntarily withdrawn if an applicant fails to respond to an approvable letter, major deficiency letter, or not approvable letter within 75 days of issuance of the letter.[53] However, if before the end of that 75-day period, an HDE applicant requests additional time to generate data or provide other information to address the issues identified in the FDA letter, FDA may agree to allow additional time, as appropriate. When additional time is requested, FDA generally would allow up to 360 days to provide a complete response to the FDA action letter. We generally do not find it appropriate to agree to requests for additional time beyond 360 days. FDA intends to notify the applicant with a letter acknowledging voluntary withdrawal of the HDE application or HDE supplement, and any amendment submitted in response to an FDA action letter after FDA's notification acknowledging voluntary withdrawal would be considered a resubmission of the HDE application. As such, it will be assigned a new HDE number and will be subject to the requirements of 21 CFR 814.104.

VI. Assessing Probable Benefit and Risk in an HDE Application

As discussed above, a device that meets the criteria under section 520(m) of the FD&C Act is exempt from the effectiveness requirements of sections 514 and 515 of the FD&C Act but is not exempt from the requirement for a reasonable assurance of safety.[54] To approve an HDE application, section 520(m) of the FD&C Act requires that FDA find, among other things, "that the device will not expose patients to an unreasonable or significant risk of illness or injury and the probable benefit to health from the 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 device[s] or alternative forms of treatment."[55] To make these findings and evaluate safety and probable benefit, FDA performs an assessment of probable risks and benefits for a device as part of its HDE application review.

FDA also assesses probable benefits and risks as part of its review of PMAs and De Novo requests,[56] and the Agency has previously presented a benefit-risk framework for benefit-risk

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[53] See 21 CFR 814.106.

[54] See sections 514, 515, and 520(m) of the FD&C Act; 21 CFR 814.118(a)(1). FDA regulations state that there is a reasonable assurance that a device is safe "when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks." 21 CFR 860.7(d)(1).

[55] Section 520(m)(2)(C) of the FD&C Act.

[56] See FDA's guidance, "Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications," (https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm517504.pdf) for a discussion of how FDA benefit-risk

determinations in the context of reviewing those applications in the guidance document "Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications." FDA believes that the benefit-risk framework and factors used to assess PMAs or De Novo requests referenced above is generally appropriate for HDE applications. FDA therefore intends to consider the same factors described in FDA's benefit-risk framework for evaluating PMAs or De Novo requests when assessing probable benefits and risks for HDE applications.

However, given the different standards and requirements that apply to approval of an HDE application, the weighting of those factors and the nature of the evidence available regarding those factors is likely to differ in the HDE context. Among other differences, a reasonable assurance of effectiveness is not required for a device approved under an HDE application.[57] Therefore, when compared to a PMA or De Novo request, both of which require a demonstration of reasonable assurance of safety and effectiveness,[58] there is generally likely to be greater uncertainty surrounding the benefit-risk profile based on the evidence submitted in an HDE application.

Moreover, as with the benefit-risk framework for evaluating PMAs or De Novo requests, FDA considers relevant factors as part of the probable benefit-risk assessment for an HDE application in the context of the intended use of the device, including the target patient population and the size of the population. FDA's probable benefit-risk assessment also takes into account currently available alternative treatments or diagnostics, including their limitations. When available, information characterizing patients' tolerance for risk and their perspective on probable benefit may provide useful context during this assessment. Refer to the FDA guidance document, "Patient Preference Information—Voluntary Submission, Review in Premarket Approval Applications, Humanitarian Device Exemption Applications, and De Novo Requests, and Inclusion in Decision Summaries and Device Labeling."[59]

The Agency's probable benefit-risk framework provides for flexibility and use of scientific judgment in assessing the totality of the evidence to determine if a specific device meets the standard for HDE application approval. This flexibility allows FDA to take into account considerations relevant to HDE applications (e.g., a relatively small patient population) under a framework that is consistent across device marketing submission types. To do so, FDA has developed tools to assist in assessing probable benefit and risk for an HDE application. Refer to the supplementary Considerations for the Probable Benefit-Risk Assessment in Appendix B and

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assessments relate to the Agency's safety and effectiveness evaluation of a device in the context of reviewing PMAs and De Novo requests.

[57] Section 520(m)(2) of the FD&C Act.

[58] To meet the statutory standard for approval of a PMA, there must be a showing of reasonable assurance that the device is safe and effective. See section 515(d) of the FD&C Act. The De Novo classification process is appropriate for devices that would otherwise be subject to PMA but for which general controls or general and special controls provide a reasonable assurance of safety and effectiveness. See section 513(f)(2) of the FD&C Act.

[59] Available at https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM446680.pdf.

the Probable Benefit-Risk Assessment Tool in Appendix C. These tools are intended to reflect differences in probable benefit-risk determinations for an HDE application when compared to other types of device marketing submissions. Note that the tools in this draft guidance also present questions to consider regarding the factors for the probable benefit-risk assessment differently than the benefit-risk guidance for PMAs and De Novos. While the factors have the same meaning, the tools for HDE applications have been reorganized to assist in weighing the probable benefits and risks.

FDA has also published guidance with respect to making benefit-risk determinations for IDE applications.[60] However, unlike an IDE, which permits a device to be shipped lawfully for the purpose of conducting a clinical investigation of the device's safety and/or effectiveness, an approved HDE application is a marketing authorization. Accordingly, the two applications have different statutory and regulatory standards and, as a general matter, earlier stages of device development and investigational study under an IDE are typically associated with greater uncertainty than an HDE. Approval of an IDE application to permit investigational use of a device may be appropriate where it is unknown if subjects are likely to benefit from the use of the device, if the risks to the subjects are outweighed by the anticipated benefits to the subjects and the importance of the knowledge to be gained, and the IDE application otherwise satisfies the requirements of 21 CFR part 812.[61] In contrast, approval of the HDE application, which authorizes the marketing of a device, requires, among other things, a demonstration that there is probable benefit and that the probable benefit 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.

For HDE applications, probable benefit is present when there is evidence for FDA to reasonably conclude that patients are likely to benefit from the use of the device. The probable benefit-risk decision support tools prompt FDA review staff to consider probable benefit in terms of:

- Type of benefit(s)
- Magnitude of benefit(s);
- Probability of the patient experiencing one or more benefit(s);
- Duration of effect(s); and
- Patient perspectives.

In addition, the probable benefit-risk decision support tools prompt FDA review staff to consider risk in terms of:

- Severity, types, number and rates of harmful events associated with use of the device;

[60] See "Factors to Consider When Making Benefit-Risk Determinations for Medical Device Investigational Device Exemptions," (https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM451440.pdf).

[61] FDA may disapprove or withdraw approval of an IDE application if, among other reasons, "[t]here is reason to believe that the risks to the subjects are not outweighed by the anticipated benefits to the subjects and the importance of the knowledge to be gained . . . ." 21 CFR 812.30(b)(4).

- Probability of a harmful event;
- Duration of harmful events;
- Risk from false-positive or false-negative results for diagnostics; and
- Patient perspective.

As with benefit-risk assessments for PMAs and De Novo requests, FDA considers additional factors, including uncertainty and available alternative treatments or diagnostics, as part of assessing whether probable benefits outweigh the probable risks in the context of an HDE application. Sources of evidentiary uncertainty could include, but are not limited to:

- Sample size;
- Duration of follow-up;
- Use of a surrogate outcome; and/or
- Use of non-clinical performance data such as animal testing or computer modeling rather than or in addition to a clinical or surrogate outcome.

FDA recognizes that in some instances there may be little or no clinical experience with the device that is the subject of an HDE application. Depending upon the nature of the device and its associated risks, FDA may request that clinical data be collected in support of an HDE application. However, it is also important to recognize that non-clinical data may play a critical role in probable benefit-risk assessments in the context of HDE. Medical devices often have attributes that cannot be tested by clinical methods alone and that play a major role in the performance, safety, or effectiveness of the device. In some cases, non-clinical testing (e.g., engineering performance studies, animal studies, analytical testing, or computer modeling and simulation) can obviate or reduce the need for clinical testing to evaluate certain aspects of device design or performance. Both clinical and non-clinical testing methods may be used to assess the probable benefit (including consideration of its likelihood, magnitude and duration), the probability or severity of a given risk, and/or the success of risk control measures, including risk mitigation measures.

The document at Appendix B, "Considerations for the Probable Benefit-Risk Assessment," is intended to complement the Probable Benefit-Risk Assessment Tool at Appendix C. When finalized, FDA staff should use the two tools together while reviewing the HDE application. FDA staff should also refer to this guidance, when finalized, to assist them in making their determinations. HDE applicants may also consider these tools, but inclusion of these documents as part of an application is not a requirement.

VII. Post-Approval Requirements

HDE applications are subject to a number of post-approval requirements, as described below. In addition to these requirements, a post-approval study (PAS) may be required and described in the

approval order.[62] The guidance document, "Procedures for Handling Post-Approval Studies Imposed by PMA Order," includes recommendations for PMA post-approval studies.[63] However, most of the information in this guidance document also applies to post-approval studies imposed for an approved HDE application.

A. IRB or Appropriate Local Committee Oversight and Approval

A HUD with an approved HDE application is approved by FDA for marketing. However, the HDE holder is responsible for ensuring that a HUD under an HDE is administered only in facilities having IRB oversight in accordance with the Agency's regulation governing IRBs.[64] In addition, approval by an IRB or an appropriate local committee is required before a HUD under an HDE can be used at a facility for clinical care, with the exception of emergency use.[65] See Section VIII.G., "Emergency Use of HUDs." Note that an IRB or appropriate local committee is not required to review and approve each individual use of a HUD and may grant a generalized approval to use the HUD at a facility. In such circumstances, FDA does not require the facility, HDE holder, or practitioner to seek approval from the IRB or appropriate local committee for each use, provided the use of the HUD is within the terms of the generalized approval.

The HDE holder is not required to submit the names and addresses of the reviewing IRBs or appropriate local committees to FDA. However, as required in 21 CFR 814.126(b)(2), the HDE holder must maintain records of:

- The names and addresses of the facilities to which the HUD was shipped;
- Correspondence with reviewing IRBs; and
- Any other information requested by a reviewing IRB or FDA.

FDA recommends that HDE holders likewise maintain correspondence with reviewing appropriate local committees as well as other information that such committees may require. Additional information regarding the role of IRBs and appropriate local committees with respect to HUDs is available in Section VIII.E, below.

B. Adverse Event Reporting

Whether expected or not, adverse events must be reported and evaluated in accordance with Medical Device Reporting requirements in 21 CFR part 803. Device manufacturers and user facilities are required to submit medical device reports to FDA and to the "IRB of record" (i.e., the IRB that oversees use of the HUD at the facility where the adverse event occurred) after

[62] 21 CFR 814.126(a) and 814.82(a)(2).
[63] Available at https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071013.pdf.
[64] See section 520(m)(4)(A) of the FD&C Act. FDA regulations governing IRBs are in 21 CFR part 56.
[65] See section 520(m)(4)(B) of the FD&C Act and 21 CFR 814.124(a).

HDE approval.[66] In the event that an appropriate local committee approved the use of the HUD for routine clinical care at that facility, instead of an IRB, we recommend that manufacturers submit MDRs to that committee.

Accordingly, manufacturers must submit MDRs to FDA and the IRB of record when they become aware of information reasonably suggesting that a HUD may have caused or contributed to a death or serious injury, or has malfunctioned and would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.[67]

User facilities must submit MDRs to FDA, the IRB of record, and the manufacturer when they become aware of information reasonably suggesting that a HUD may have caused or contributed to the death of a patient, and must submit reports to the manufacturer (or to FDA and the IRB of record if the manufacturer is unknown) when they become aware of information reasonably suggesting that a HUD may have caused or contributed to a serious injury to a patient of the facility.[68] As defined by 21 CFR 803.3(w), a serious injury means an injury or illness that:

- Is life-threatening;
- Results in permanent impairment of a body function or permanent damage to a body structure; or
- Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

Pediatric adverse events will be reviewed periodically by FDA's Pediatric Advisory Committee (PAC).[69]

If the HUD is being investigated in a clinical study under an IDE, adverse events that occur during the study should be reported in accordance with 21 CFR 812.150(a)(1) and 812.150(b)(1).

C. HDE Supplements

After FDA approval of an original HDE application, an applicant shall submit an HDE supplement for review and approval by FDA before making a change affecting the safety or probable benefit of the device.[70]

If you wish to request new indications for use for a device under an HDE (e.g., for a different disease or condition) you must obtain a new HUD designation and submit a new original HDE application in compliance with 21 CFR 814.110. If you are submitting a new original HDE application, please contact OOPD to discuss obtaining a new HUD designation. In the new HDE

[66] See section 519(a) and (b) of the FD&C Act; 21 CFR 803.30, 803.50, and 814.126(a). See 21 CFR 803.3(d) for the definition of a device user facility.
[67] See 21 CFR 803.50.
[68] 21 CFR 803.30.
[69] Section 520(m)(8) of the FD&C Act.
[70] 21 CFR 814.108 and 814.39.

application, any relevant information or data submitted in the HDE application for the original indication may be incorporated by reference.

D. HDE Periodic Reports

You must submit periodic reports for HDEs in accordance with the approval order under 21 CFR 814.126(b). HDE periodic reports must include the following information unless FDA specifies otherwise:

- An update of the information required under 21 CFR 814.102(a) to demonstrate that the HUD designation is still valid.[71] An updated annual incidence reassessment (AIR) based on updated numbers to show that the target population for the disease or condition for which the device has been designated is not more than 8,000 per year provides this information. The AIR refers to the HUD designated population, which in some cases may be larger than the approved indication under the HDE (i.e., if the HDE approval covers only a certain indication within the designated disease or condition). In reviewing this information, the reviewing center, CDRH or CBER, may refer the AIR to OOPD for further evaluation if necessary.
- An update to the explanation of why the device would not be available unless an HDE were granted, a statement that no other comparable device (other than another HUD under an HDE or a device under an IDE) is available to treat or diagnose the disease or condition, and an updated discussion of the risks and benefits of currently available devices or alternative forms of treatment in the United States.[72]
- An update to the explanation of why the probable benefits to health from the 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.[73]
- An update to the amount to be charged for the device and, if over $250, a report by an independent certified public accountant or an attestation by a responsible individual of the organization verifying that the amount charged does not exceed the costs of the device's research, development, fabrication, and distribution.[74]
- The number of devices that have been shipped or sold since initial marketing approval and, if the number shipped or sold exceeds 8,000, an explanation and estimate of the number of devices used per patient.[75] FDA interprets this regulation to require HDE holders to report the total number of HUDs shipped or sold pursuant to the approved HDE application, no matter how the HUDs are used (whether for the approved indication(s), emergency use, or otherwise). However, for devices that have both an HDE application approval and a PMA approval for a different indication, you need report only

[71] See 21 CFR 814.126(b)(1)(i).
[72] See 21 CFR 814.126(b)(1)(ii) and 814.104(b)(2).
[73] See 21 CFR 814.126(b)(1)(ii) and 814.104(b)(3).
[74] See 21 CFR 814.126(b)(1)(ii) and 814.104(b)(5).
[75] See 21 CFR 814.126(b)(1)(iii).

the number of devices that are shipped or sold pursuant to the HDE unless specifically required otherwise by the PMA Approval Order.

- Information describing the clinical experience with the approved device, including safety information that is known or reasonably should be known to the applicant, and any medical device report made under 21 CFR part 803.[76]
- A summary of any changes made to the device in accordance with supplements submitted under 21 CFR 814.108.[77]

E. HUD Designation Re-Evaluation

If, based on information contained in the HDE periodic reports, FDA is concerned that the HUD designation may no longer apply to your device, we may contact you for additional information, re-evaluate, and possibly revoke your HUD designation.[78]

If we make the determination that more than 8,000 individuals in the United States are affected by or manifest a certain disease or condition per year, we may consider whether your HUD designation should be revoked in accordance with 21 CFR 814.102(c) and your HDE withdrawn in accordance with 21 CFR 814.118. In making this determination, we intend to consider factors such as the number of patients with the disease or condition and the public health need for the device. We intend to discuss the regulatory options with the HDE holder before revoking a HUD designation. The investigational use of a HUD outside of the HUD designation would not count toward the limit of 8,000 individuals per year.

If FDA subsequently approves a PMA or grants a De Novo request for the HUD or another comparable device with the same indication(s), we may withdraw the HDE because the HUD would no longer meet the requirements of section 520(m)(2)(B) of the FD&C Act.[79]

VIII. Special Considerations for Devices Marketed Under an HDE

A. Eligibility for Profit

Except in certain circumstances, HUDs under an HDE cannot be sold for an amount that exceeds the costs of research and development, fabrication, and distribution of the device (i.e., for profit). If a HUD is studied in a clinical investigation for a new indication, the sponsor of the clinical investigation cannot charge subjects or investigators a price higher than necessary to recover the costs of manufacture, research, development, and handling.[80] Any costs for which a subject in a

[76] See 21 CFR 814.126(b)(1)(iv).
[77] See 21 CFR 814.126(b)(1)(v).
[78] See 21 CFR 814.102(c) and 814.126(b)(1).
[79] See 21 CFR 814.118(a).
[80] See 21 CFR 812.7(b).

clinical investigation is responsible must, when appropriate, be provided in the informed consent document.[81]

Under section 520(m)(6)(A)(i) of the FD&C Act, as amended by FDASIA, a HUD under an HDE is only eligible to be sold for profit if the device meets the following criteria (i.e., the eligibility criteria):

- The device is intended for the treatment or diagnosis of a disease or condition that occurs in pediatric patients or in a pediatric subpopulation, and such device is labeled for use in pediatric patients or in a pediatric subpopulation in which the disease or condition occurs; or
- The device is intended for the treatment or diagnosis of a disease or condition that does not occur in pediatric patients or that occurs in pediatric patients in such numbers that the development of the device for such patients is impossible, highly impracticable, or unsafe.

If a device under an HDE does not meet either of the eligibility criteria, the device cannot be sold for profit. FDA reviews the financial information in the HDE holder's initial application and periodically thereafter. When approving the use of a HUD for treatment or diagnosis of patients in clinical care, the IRB or appropriate local committee is not required to review a justification for the amount charged for the HUD. The descriptions below are intended to provide additional clarity regarding each component of the eligibility criteria.

Occurs in pediatric patients or in a pediatric subpopulation – This would be a disease or condition that occurs in patients who are younger than 22 years of age.

Does not occur in pediatric patients – This would be a disease or condition that occurs only in patients who are 22 years of age or older. An example of a disease that does not occur in pediatric patients is Alzheimer's disease.

Impossible or highly impracticable – When determining whether the development of a HUD in pediatric patients is "impossible" or "highly impracticable," FDA considers information provided by the applicant to FDA, including publicly-available information such as published literature, which demonstrates that the sponsor would not be able to conduct the necessary clinical investigation(s) in the pediatric population for the device.

For example, FDA may determine that the development of a particular device is "impossible" or "highly impracticable" in pediatric patients if the device is intended to treat a disease or condition that has a pediatric annual incidence that is so small, or if the prevalence of the pediatric patients living with the disease is so small, or if the pediatric population is so geographically dispersed to prevent sufficient patient recruitment in the pediatric population for a clinical investigation. Because of the speed and efficiency of

[81] 21 CFR 50.25(b)(3).

modern communications tools, geographic dispersion will justify a waiver only in extraordinary circumstances and will generally have to be coupled with very small population size. FDA does not consider economic factors (such as the costs associated with conducting a clinical investigation) as a basis for being "impossible" or "highly impracticable."

Unsafe – FDA may determine that the development of a HUD in pediatric patients is "unsafe" if the applicant has provided information, including publicly-available information such as published literature, to FDA that demonstrates that the device would expose pediatric patients to an unreasonable or significant risk of illness or injury. If FDA determines that the HUD is eligible to be sold for profit because development of the device in pediatric patients would be "unsafe," the labeling (e.g., warnings or contraindications) for the device should reflect the safety concern.

An HDE applicant whose device meets one of the eligibility criteria and who wishes to sell its HUD for profit should provide adequate supporting documentation to FDA in its original HDE application to demonstrate to FDA that the HUD meets the eligibility criteria. An HDE holder whose HDE application was approved prior to the enactment of FDASIA on July 9, 2012, and who wishes to sell its HUD for profit should provide adequate supporting documentation to FDA in an HDE supplement to demonstrate to FDA that the HUD meets the eligibility criteria. If FDA determines that the HUD meets the eligibility criteria, FDA will then determine the ADN for the HUD when FDA approves the HDE application or supplement.[82]

B. The Annual Distribution Number (ADN)

Under section 520(m)(6) of the FD&C Act, if FDA makes a determination that a HUD meets the eligibility criteria, you may sell the HUD for profit after receiving HDE application approval as long as the number of devices distributed in any calendar year does not exceed the ADN for the device.

The ADN is determined by FDA:

- When the Agency approves the original HDE application; or
- When the Agency approves an HDE supplement for an HDE application approved before the enactment of FDASIA on July 9, 2012, if the HDE holder seeks a "determination" for the HUD in an HDE supplement based upon the profit-making eligibility criteria, and FDA determines that the HUD meets the eligibility criteria.[83]

Under section 520(m)(6)(A)(ii) of the FD&C Act, the ADN is defined, with respect to a device under an HDE, as the number of devices "reasonably needed to treat, diagnose, or cure a population of 8,000 individuals in the United States." The applicant should provide the number

[82] See section 613(b) of FDASIA and Section VIII.B. for more discussion on the ADN.
[83] See section 520(m)(6)(A)(ii) of the FD&C Act and section 613(b) of FDASIA.

of devices per year reasonably needed for each individual in the HDE application or HDE supplement and provide adequate supporting documentation to support such number in order to provide a basis for FDA to calculate the ADN.

When determining the ADN, FDA considers the number of devices per year reasonably needed to treat, diagnose, or cure an individual ("first multiplier") and multiplies that value by 8,000 ("second multiplier"). By law, the second multiplier is always 8,000. Therefore, the ADN will be equal to or greater than 8,000, depending on the value of the first multiplier. For example, the target population estimate for the intended use may be 3,000 individuals, but if 2 devices are reasonably needed per year to treat, diagnose or cure a patient, the ADN would be 16,000 (i.e., 2 multiplied by 8,000 because the second multiplier for the ADN is always 8,000, regardless of the actual population estimate). After FDA has determined the ADN, an HDE holder may submit an HDE supplement requesting that FDA modify the ADN based upon additional information, and FDA may modify the number.[84]

As required under 21 CFR 814.126(b)(1)(iii), the HDE holder (applicant) is responsible for monitoring how many devices are shipped or sold each year, and if that number exceeds 8,000, to provide an explanation and estimate to FDA of how the device is being used by patients. Similarly, the HDE holder is responsible for monitoring when the number of devices shipped or sold in a year exceeds the ADN, when the HUDs are approved by FDA to make a profit.[85] An IRB or appropriate local committee is not responsible for monitoring the number of uses per year of the HUD.

If the HDE holder ships multiple sizes of a device to help ensure that one of the devices is the appropriate size for the patient(s) when used, it would not be necessary to count all of these devices toward the ADN tally if the additional sizes of the devices (that did not properly fit the patient(s)) are returned to the HDE holder. Unused devices should be returned to the HDE holder to appropriately account for them. The HDE holder should document in its periodic report how many devices are returned to the HDE holder if multiple sizes are shipped. Additionally, HDE holders should keep in mind that if they distribute devices in excess of the ADN, they will not be able to make a profit on those devices.

HDE holders assigned an ADN must immediately notify the Agency if the number of devices distributed in a calendar year exceeds the ADN.[86] FDA interprets this statutory requirement to mean that HDE holders must immediately notify the Agency by submitting an HDE report whenever the number of HUDs shipped or sold in a calendar year, however the HUD is used, exceeds the ADN. The statutory notification requirement is generally consistent with the reporting requirement in 21 CFR 814.126(b)(1)(iii) concerning the number of devices shipped or sold regardless of their ultimate use (even if outside their approved indications). However, the statutory provision requires immediate notification when the number shipped or sold in a

[84] See section 520(m)(6)(C) of the FD&C Act.
[85] See section 520(m)(6)(A)(iii) of the FD&C Act.
[86] See section 520(m)(6)(A)(iii) of the FD&C Act.

calendar year exceeds the ADN, whereas the current HDE regulations require periodic reports on a timeframe specified in the HDE approval order.

Once this notification occurs, or once FDA discovers through an inspection that the ADN has been exceeded, then the sales of the HUD for the remainder of the year are subject to the general prohibition on profit (unless FDA approves an ADN modification request in an HDE supplement), and the amount charged for the device must not exceed the cost of research and development, fabrication, and distribution of the device.[87]

In those cases in which a device is approved for a certain indication under an HDE application and is approved for a different indication under a PMA or De Novo request, sales or shipments of the device pursuant to the PMA or the De Novo request are not subject to the ADN reporting requirement. The ADN relates only to those devices that are marketed under an HDE. Therefore, the manufacturer is required to notify FDA only when sales or shipments pursuant to the HDE exceed the ADN. If a manufacturer must report the number of sales or shipments of a device approved for certain indications under a PMA, the manufacturer would be responsible for separately reporting sales or shipments of devices marketed for different indications under an HDE per 21 CFR 814.126(b)(1)(iii).

C. Information to Patients

Neither the FD&C Act nor FDA regulations require informed consent from patients who are treated or diagnosed with an HDE-approved HUD in the course of their clinical care. An IRB or appropriate local committee may, however, choose to require that patients receive certain information about the HUD when the committee approves use of the HUD for clinical care at a facility. If a committee requires that patients receive a written document prior to use of the HUD in clinical care, the document should include much of the information found in the HDE patient labeling. If no patient information packet is available, the HDE holder may consider including the following in any written information provided to patients: an explanation that the HUD is designed to diagnose or treat the disease or condition described in the HDE labeling and that no comparable device is available to treat the disease or condition; a description of any ancillary procedures associated with the use of the HUD; a description of the use of the HUD; all known risks or discomforts; and an explanation of the postulated mechanism of action of the HUD in relation to the disease or condition. The IRB or appropriate local committee may decide to require inclusion of this or other information explicitly as part of a written document provided to patients.

The labeling for a HUD approved under an HDE, including any labeling provided to patients, must be truthful and non-misleading.[88] The device labeling must also include the following statement clarifying that effectiveness has not been demonstrated: "Humanitarian Device. Authorized by Federal law for use in the [treatment or diagnosis] of [specify disease or

[87] See section 520(m)(6)(D) of the FD&C Act.
[88] See section 502(a) of the FD&C Act, 21 U.S.C. 352(a).

condition]. The effectiveness of this device for this use has not been demonstrated."[89] Additional labeling requirements appear under 21 CFR 814.20(b)(10).

D. HDEs and Pediatric Patients

As discussed above, under section 520(m)(6)(A)(i)(I) of the FD&C Act, a HUD is eligible to be sold for profit if, among other things, the device is "intended for the treatment or diagnosis of a disease or condition that occurs in pediatric patients or in a pediatric subpopulation, and such device is labeled for use in pediatric patients or in a pediatric subpopulation in which the disease or condition occurs." This provision permits HDE holders to receive a profit from the sale of HUDs that are indicated and labeled for pediatric use, subject to the limit of the ADN.

HUDs marketed under an HDE may be indicated and labeled for pediatric use only or for use in both pediatric and adult patients. Devices that are intended to treat both a pediatric population and an adult population may be included in a single HDE application, but the indications for use should specify use in pediatric patients, or pediatric subpopulation(s), as well as use in adults. In some cases, the probable benefit-risk profile for devices intended for use in a pediatric population, or in a pediatric subpopulation, may differ from its profile when intended for use in an adult population. Therefore, we recommend that HDE applications for devices intended for use in pediatric populations and in adult populations include data supporting the use in both pediatric and adult populations or an appropriate rationale specifically addressing how the data provided for one population (e.g., adults) are sufficient to support approval of an HDE application with indications for use in both populations. For more information about extrapolating data, refer to the FDA guidance, "Leveraging Existing Clinical Data for Extrapolation to Pediatric Uses of Medical Devices."[90]

As defined in section 520(m)(6)(E)(i) of the FD&C Act, pediatric patients for purposes of section 520(m) of the FD&C Act are patients who are 21 years of age or younger (i.e., up to, but not including, the 22nd birthday) at the time of the diagnosis or treatment.[91] As defined by section 520(m)(6)(E)(ii) of the FD&C Act, "pediatric subpopulation" means one of the following populations: neonates, infants, children, or adolescents. Additional information about the definition of pediatric patients and pediatric use as it relates to medical devices can be found in the FDA guidance, "Premarket Assessment of Pediatric Medical Devices."[92]

HUDs that are approved and labeled for pediatric patients or in a pediatric subpopulation as described in section 520(m)(6)(A)(i)(I) of the FD&C Act are required, under section 520(m)(8)

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[89] 21 CFR 814.104(b)(4)(ii).
[90] Available at https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM444591.
[91] See also 21 CFR 814.3(s).
[92] Available at https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089742.pdf.

of the FD&C Act, to be reviewed annually by FDA's PAC.[93] The PAC annually reviews these HUDs to ensure that the HDE remains appropriate for the pediatric populations for which it was approved. The PAC also conducts periodic review of adverse events for these devices.[94]

E. Review and Approval of the Use of HUDs in Clinical Care

As summarized above, an IRB or appropriate local committee must approve the use of a HUD at a given facility before it can be used at that facility.[95] Therefore, a health care provider wishing to use an HDE-approved HUD to treat or diagnose a patient at a facility should obtain approval from the facility's IRB or the appropriate local committee before use of the HUD, except in certain emergencies where prior approval is not required. See Section VIII.G., "Emergency Use of HUDs." In reviewing the use of the HUD in clinical care, the IRB or appropriate local committee should be cognizant that FDA has made a determination of safety and probable benefit for use of the HUD only within its approved indication(s).

The HDE holder is responsible for ensuring that the HUD is administered in facilities that have oversight by an IRB constituted and functioning in accordance with 21 CFR part 56.[96] Note that an IRB's or the appropriate local committee's approval for the "use" of a HUD at a facility to treat or diagnose patients in the course of providing clinical care does not mean that there has been IRB approval of a clinical investigation involving the HUD.

FDA interprets the statutory term "appropriate local committee" to mean a standing committee for the facility that has expertise and experience in reviewing and making treatment decisions for clinical care, particularly in applying innovative medical device technologies to clinical care. As such, a standing committee for the facility that includes physicians with experience in the treatment of rare diseases or conditions would be considered an appropriate local committee by the Agency. Depending on the facility and the charters of its committees, examples of an appropriate local committee may include a peer review committee, a credentialing committee, or a Quality Care Committee. We recommend that the committee include the chief medical officer or the departmental chief. In addition, FDA interprets the term "appropriate" to mean that members of the appropriate local committee are free of financial and other conflicts of interest in decisions pertaining to the use of the HUD in clinical care or they recuse themselves from such decisions in which they have a conflict of interest. Merely because a facility has a standing committee does not mean the committee is appropriate to review use of a HUD in clinical care.

The IRB or appropriate local committee is not required to review and approve each individual use of a HUD, nor is it required to audit medical records of patients who receive a HUD. Rather,

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[93] For more information on the PAC, see https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/default.htm.

[94] See section 520(m)(7) of the FD&C Act.

[95] Section 520(m)(4)(B) of the FD&C Act.

[96] See section 520(m)(4)(A) of the FD&C Act and 21 CFR 814.124(a).

the IRB or appropriate local committee may use its discretion to determine how to approve use of a HUD, including consideration of providers' qualifications through training and expertise to use the device.[97] For example, with the input of members with the appropriate expertise in the clinical area, an IRB or appropriate local committee may specify limitations on the use of the device based upon one or more measures of disease progression, prior use and failure of any alternative treatment modalities, reporting requirements to the committee or committee chairperson, appropriate follow-up precautions and evaluations, or other criteria the committee determines to be appropriate.

1. Process and Considerations for Reviewing the Use of HUDs in Clinical Care

For initial review of a HUD, the IRB or appropriate local committee should perform its review at a convened meeting of the committee.[98] The IRB or appropriate local committee should have policies and procedures in place for the receipt and evaluation of the materials necessary for initial approval and continuing review of the HUD's use at that facility. The policies and procedures should also specify whether the committee requires a consent document for the use of the HUD at that facility.

FDA recommends that the IRB or appropriate local committee follow the review criteria in 21 CFR 56.111 and elsewhere in part 56, where applicable. For example, the IRB or appropriate local committee should review the risks to patients that are found in the HDE-approved product labeling, ensure the risks are minimized, and evaluate whether the risks are reasonable in relation to the proposed use of the device at the facility. FDA also recommends that the IRB or appropriate local committee review the following materials, as applicable, during initial review of a request to use a HUD:

- A copy of the HDE approval order;
- A description of the device;
- The product labeling;
- The patient information packet that may accompany the HUD;
- A sample consent form for the use of the HUD in clinical care, if required by the IRB or appropriate local committee or by facility policy; and
- A summary of how the physician proposes to use the device, including a description of any screening procedures, the HUD procedure, and any patient follow-up visits, tests or procedures.

[97] For many HDE-approved HUDs, the HDE holder is required to provide training on the use of the device prior to the health care provider using the device. Such requirements would be specified in the HDE application approval order. See 21 CFR 814.126(a) and 814.82(a).

[98] See 21 CFR 56.108, which describes a convened meeting of an IRB for purposes of reviewing FDA-regulated clinical investigations.

A list of approved HDE applications may be found at https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/HDEApprovals/default.htm. The approval order, labeling, and patient information may be found by selecting the submission number of the appropriate HDE application.

FDA does not require submission of a protocol to the IRB or appropriate local committee for review when the committee is evaluating a request to use the HUD in the clinical care of patients at a facility. However, the IRB, appropriate local committee, or institution may require one under its own policies and procedures.

In addition, FDA does not require committees other than the IRB or appropriate local committee to approve the use of a HUD. However, the institution may require additional review. For example, the use of another committee to provide assessments of specific risks posed by the technology or software compatibility may supplement the IRB or appropriate local committee review.

If a physician wants to use a HUD outside its approved indication(s), FDA recommends that the physician follow the IRB or appropriate local committee's requirements for use of a HUD at that facility, which may include separate approval requirements for use outside the approved indication(s). The IRB or appropriate local committee may also require that the physician obtain informed consent[99] from the patient and ensure that reasonable patient protection measures are followed, such as devising schedules to monitor the patient, taking into consideration the patient's specific needs, and the limited information available about the risks and probable benefits of the device. The extent of oversight in these circumstances is up to the IRB or appropriate local committee. As discussed above, MDRs must be submitted to FDA and to the "IRB of record" (i.e., an IRB approving the use of the HUD at the relevant facility) if the device may have caused or contributed to death or serious injury and for certain malfunctions. If an appropriate local committee approved the use of the HUD at the facility, FDA recommends that MDRs be submitted to that committee.

2. Continuing Review of the Use of HUDs in Clinical Care

Under FDA's current regulations, an IRB that reviews a request to use a HUD at a facility is responsible for initial as well as continuing review of the HUD.[100] When an appropriate local committee conducts such an initial review instead of an IRB, that appropriate local committee should also conduct continuing review of the HUD. For continuing review, an IRB may use an expedited review procedure in which a chairperson or one or more experienced reviewers carries out the review, similar to the expedited review procedure described at 21 CFR 56.110(b). When

[99] As noted above, "informed consent" required by a facility in the context of clinical care does not refer to informed consent subject to the requirements in FDA's regulations.

[100] 21 CFR 814.124(a).

an IRB conducts the initial review, a facility may decide to utilize an appropriate local committee to conduct continuing review of the use of the HUD in clinical care.

Appropriate local committees may develop their own policies and procedures for continuing review of a HUD and should determine what type of review procedure is appropriate for each HUD. An expedited procedure, such as that described under 21 CFR 56.110, may be appropriate for continuing review because a HUD marketed under an HDE is a legally marketed device, and its use in clinical care does not constitute "research." An expedited review does not mean a less-than-substantive review. The individual(s) conducting an expedited review for use of a HUD at a facility should thoughtfully consider the risk and benefit information available and any MDRs.

In addition, FDA does not require that the IRB or appropriate local committee serve as a Data Monitoring Committee. The IRB or appropriate local committee may, however, ask the HDE holder for copies of the safety information submitted to FDA in the periodic reports required by 21 CFR 814.126(b)(1). In this way, information that could have a bearing on human safety would be considered at the time of continuing review.

When an IRB or appropriate local committee is deciding whether to approve the use of a HUD for clinical care of patients at a facility, it does not make a Significant Risk/Non-Significant Risk (SR/NSR) determination. As noted above, use of a legally marketed HUD within its HDE-approved indication at a facility to treat or diagnose patients is not a clinical investigation of a device under 21 CFR part 812.

F. Review and Approval for Clinical Testing of HUDs

Clinical investigation of a HUD under an IDE must be approved and supervised by an IRB.[101] Data may be collected in a clinical investigation **for the HDE-approved indication(s)** without an IDE. An approved IDE permits a device to be shipped lawfully for the purposes of conducting investigations of the device without complying with certain other requirements of the FD&C Act that would apply to devices in commercial distribution.[102] As long as the HUD is being studied for the indication(s) in its approved labeling, the HUD is not subject to IDE requirements because the HUD is a legally marketed device and therefore can be lawfully shipped without an IDE. However, regardless of the applicability of the IDE regulation at 21 CFR part 812, other FDA regulatory requirements may still apply, including among others, requirements for IRB

[101] See 21 CFR 56.103, 812.2(b)(ii), and 812.42.
[102] See 21 CFR 812.1.

review and approval, financial disclosure, informed consent[103] and, if applicable, additional safeguards for children.[104]

If the IRB receives a request to review an investigation to determine safety or effectiveness of the HUD for a different indication than the HDE-approved indication(s), then the IRB should be aware that this type of clinical investigation is subject to the IDE regulations at 21 CFR part 812. If the device is a SR device, the sponsor of the investigation must submit an IDE application to FDA and obtain FDA approval of that application before starting the clinical investigation.[105] A physician who wants to study a HUD may be the sponsor, investigator, or both for the study. In sum, the investigational use of a HUD under these circumstances must be conducted in accordance with 21 CFR parts 812, 50, 54, and 56.[106]

Significant Risk/Non-Significant Risk Determinations

An IRB does not have to make a SR/NSR determination when it receives a request to review a clinical investigation of a HUD (e.g., collection of safety and effectiveness data) when that clinical investigation concerns the HDE-approved indication(s) only. As noted above, FDA does not consider such investigations to require an IDE under 21 CFR part 812.

For an investigation of the HUD for indications other than the HDE-approved indication(s), the IRB would need to make a SR/NSR determination if that determination has not already been made by FDA.[107] In practice, most sponsors have submitted and obtained FDA approval of an IDE application before submitting such investigations of HUDs to IRBs for review, so IRBs have not needed to make the SR/NSR determination (i.e., FDA had already determined the device was a SR device). However, in the event that a sponsor seeks IRB approval for investigational use of a HUD for an indication other than its approved indication(s) without first obtaining a determination from FDA regarding whether the study is a SR or NSR study, then the IRB should make the SR/NSR determination as required in 21 CFR 812.66.

G. Emergency Use of HUDs

If a physician in an emergency situation determines that IRB or appropriate local committee approval for the use of the HUD at the facility cannot be obtained in time to prevent serious harm or death to a patient, a HUD may be used without prior approval. In this situation, the HDE

[103] Specific requirements for obtaining informed consent from human subjects apply to FDA-regulated clinical investigations. See 21 CFR part 50, subpart B. Note that, in some cases, facilities may have specific requirements for obtaining informed consent for the use of the HDE-approved HUD in the routine clinical care of patients, but these would not be FDA regulatory requirements.

[104] See 21 CFR part 56 for IRB requirements; see 21 CFR part 54 for requirements for financial disclosure by clinical investigators; and see 21 CFR part 50 for requirements for the protection of human subjects, including additional safeguards for children.

[105] 21 CFR 812.20(a).

[106] Note that 45 CFR part 46 may be applicable to research involving HUDs under certain circumstances. The applicability of those regulations is outside the scope of this draft guidance.

[107] See 21 CFR 812.66.

holder may ship the HUD, based on the physician's certification of the emergent need and representation that the physician will follow the requirements of 21 CFR 814.124(a) regarding reporting. The physician must provide notification of the use to the chairperson of the IRB or appropriate local committee, and the notification must include the identification of the patient involved, the date of the use, and the reason for the use.[108] FDA regulations require that physicians provide such notification to the chairperson of an IRB in writing within 5 days of the emergency use of the device. For facilities at which an appropriate local committee reviews the use of HUDs instead of an IRB, FDA recommends that physicians also provide the required notification of the emergency use in writing and within 5 days.

FDA further recommends that the physician submit a follow-up report on the patient's condition to the HDE holder. The HDE holder is required under 21 CFR 814.126(b) to submit annual reports, including the applicant's clinical experience with the device and the number of devices shipped or sold.

[108] See section 520(m)(4) of the FD&C Act.

Appendix A – Checklist for Filing Review for HDEs

(should be completed within 30 days of DCC receipt)

HDE Number: _____ ***Date Received:*** _____

HUD Number (from OOPD): _____

Device: _____ ***Procode:*** _____

Company Name/ Address: _____

Contact Name/Phone Numbers: _____

FDA Staff Member Name: _____

Within 15 calendar days of receipt of the HDE application, FDA staff should answer the preliminary questions below, which are used as an initial screening of the HDE application. Depending upon the answers to these preliminary questions, the remainder of the filing review may or may not be necessary. If the responses to the preliminary questions and subsequent consultation with FDA staff identified below indicate that the HDE filing review should not continue, the FDA staff member or the CBER regulatory project manager (RPM) should promptly inform the FDA team (including consulting reviewers and management) and notify the requester using proper administrative procedures.

Preliminary Questions		
Answers in the shaded blocks indicate consultation with an identified Center advisor is needed.	**Yes**	**No**
1. Is the product a device (per 201(h) of the FD&C Act) or a combination product with a device constituent part? If it appears not to be a device or such a combination product, or you are unsure, consult with the CDRH Jurisdictional Officer or CBER Product Jurisdiction Officer to determine the appropriate action and inform management. *Provide summary of Jurisdictional Officer's/Liaison's determination.* If the product does not appear to be a device or a combination product with a device constituent part, mark "No." NOTE: If the product is a combination product with a device constituent part, it may not be appropriate for review under an HDE. If the product is a combination product, consult with the CDRH Jurisdictional Officer (cdrhproductjurisdiction@fda.hhs.gov) or CBER Product Jurisdiction Officer and inform management.		
2. Is there a copy of, or reference to the determination made by the Office of Orphan Product Development that the device qualifies as a HUD? [814.104(b)(1)] If there is no copy of, or reference to the HUD determination, mark "No."		
3. If a Request for Designation (RFD) was submitted for the device and assigned to your center, identify the RFD # and confirm the following: • Is the device the same (e.g., design, formulation) as that presented in the RFD submission? • Are the indications for use for the device identified in the HDE the same as those identified in the RFD submission? If you believe the product or the indications presented in the HDE have changed from the RFD, or you are unsure, consult with the CDRH Jurisdictional Officer (cdrhproductjurisdiction@fda.hhs.gov) or CBER Product Jurisdiction Officer to determine the appropriate action and inform management. *Provide summary of Jurisdictional Officer's/Liaison's determination.* If the answer to either question above is no, mark "No."		

If the answer to 1 appears to be "No," then stop review of the HDE and issue the "Original Jurisdictional Product" letter.

If the answer to 3 appears to be "No," then stop the review and contact the CDRH Jurisdictional Officer or CBER Product Jurisdiction Officer.

4. Is the device eligible for HDE ? NOTE: If the device does not appear to be eligible for review through the HDE program because there is a comparable device available (e.g., a predicate device exists, a De Novo request has been granted for a similar device, or an approved PMA exists for a similar device), you should consult with the appropriate CDRH or CBER staff during the filing review. If you believe an application is for a device that is eligible for review through the HDE program and an exemption from the effectiveness provisions, you should (1) complete the 510(k) decision tree to document why the device would be found NSE (*attach copy*) and (2) obtain concurrence from the appropriate CDRH or CBER staff prior to the filing the original HDE.		
5. Is the applicant the subject of an Application Integrity Policy (AIP)? If "Yes", consult with the appropriate CDRH Office or CBER Office of Compliance and Biologics Quality/Division of Inspections and Surveillance/Bioresearch Monitoring Branch (OCBQ/DIS/BMB) to determine the appropriate action. Check on web at https://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/ucm134453.htm		

If the answer to 4 is "No", the FDA reviewer should consult management and other Center resources to determine the appropriate action.

If the answer to 5 is "Yes," then contact CDRH/OC/DBM – BIMO or CBER/OCBQ/DIS/BMB, provide a summary of the discussion, and indicate recommendation/action.

Inventory of Organizational and Administrative Elements (Requirements per 21 CFR 814.112 unless otherwise indicated)

Check "Yes" if item is present, "N/A" if it is not needed and "Not Present" if it is not included but needed.

				Present		Not Present (No)
	• Any "Not Present" answer may result in a "Refuse to File" decision. • Each element on the checklist should be addressed within the application. An applicant may provide a rationale for omission for any criteria that are deemed not applicable. If a rationale is provided, the criteria is considered Present ("Yes"). An assessment of the rationale will be considered during the review of the application.			Yes	N/A	
A.	HDE Content					
	1.	Are all required sections in English or accompanied with an English translation?		☐		☐
	2.	Is there a table of contents? [814.104(b)(4) and 814.20(b)(2)]		☐		☐
	3.	HDE / HUD Information				
		a.	Is there an explanation of why the device would not be available unless an HDE was granted? [814.104(b)(2)]	☐		☐
		b.	Is there a statement that no other comparable device, other than another approved HUD under an HDE or a device under an approved IDE, is available to treat or diagnose the disease or condition? [814.104(b)(2)]	☐		☐
		c.	Is there a discussion of the risks and benefits of currently available devices or alternative forms of treatment? [814.104(b)(2)]	☐		☐
		d.	Is there an explanation of why the probable benefit to health from the 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? [814.104(b)(3)]	☐		☐
		e.	Has the amount to be charged for the device been provided, and if greater than $250.00, is a report provided verifying that the amount charged does not exceed the costs of the device's research, development, fabrication, and distribution? [814.104(b)(5)]	☐		☐

Inventory of Organizational and Administrative Elements (Requirements per 21 CFR 814.112 unless otherwise indicated)									
Check "Yes" if item is present, "N/A" if it is not needed and "Not Present" if it is not included but needed.									
	• Any "Not Present" answer may result in a "Refuse to File" decision. • Each element on the checklist should be addressed within the application. An applicant may provide a rationale for omission for any criteria that are deemed not applicable. If a rationale is provided, the criteria is considered Present ("Yes"). An assessment of the rationale will be considered during the review of the application.							**Present**		**Not Present (No)**
								Yes	**N/A**	
	4.	Is a bibliography provided? [814.104(b)(4) and 814.20(b)(8)(i)]						☐	☐	☐
		a.	Have copies of key articles been provided and are English translations included, if appropriate? Check "N/A" if applicant includes a statement that upon searching they found no literature related to their device					☐	☐	☐
	5.	If a device sample has been requested by FDA, has it been provided or if impractical to submit, has the applicant offered alternatives to allow FDA staff to view or access the device? [814.104(b)(4) and 814.20(b)(9)]						☐	☐	☐
	6.	Is there a summary of the contents of the HDE? [814.104(b)(4) and 814.20(b)(3)]						☐		☐
	7.	Device Characteristics								
		a.	Is a description of the device included? [814.104(b)(4) and 814.20(b)(4)]					☐		☐
			i.	Pictorial representations? [814.104(b)(4) and 814.20(b)(4)(i)]				☐		☐
			ii.	Materials specifications? [814.104(b)(4) and 814.20(b)(4)(i)-(ii)]				☐		☐
				• If there is a color additive present: • has the color additive been identified by common name and chemical name, and • has the amount of each color additive in the formulation by weight percent of the colored component and total amount (e.g., ppm, µg) in the device been provided?				☐	☐	☐
		b.	Is a description of the principles of operation of the device (including components) and properties relevant to clinical function present? [814.104(b)(4) and 814.20(b)(4)(iii)-(iv)]					☐		☐
	8.	Is the Device Manufacturing Section included (see the FDA guidance, "Quality System Information for Certain Premarket Application Reviews," https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070899.pdf) [814.104(b)(4) and 814.20(b)(4)(v)]						☐		☐
		a.	Has a description of the methods, facilities, and controls used in the manufacture, processing, packing, storage, and installation of the device been provided?					☐		☐
	9.	The application includes a summary and full study report* for each nonclinical study provided? [814.104(b)(4) and 814.20(b)(6)(i)] Note: the applicant can reference data located in other applications. Check "Yes" if nonclinical data is not provided in the current application but found in another application. State where the data were provided (e.g., modular application, master file). *Full study report includes objective of the test, description of test methods and procedures, study endpoint(s), pre-defined pass/fail criteria, results summary, and discussion of conclusions. In the event that an applicant is appropriately declaring conformity with a voluntary consensus standard to meet applicable requirements, full test							☐	☐	☐

Inventory of Organizational and Administrative Elements (Requirements per 21 CFR 814.112 unless otherwise indicated)							
Check "Yes" if item is present, "N/A" if it is not needed and "Not Present" if it is not included but needed.							
	• Any "Not Present" answer may result in a "Refuse to File" decision. • Each element on the checklist should be addressed within the application. An applicant may provide a rationale for omission for any criteria that are deemed not applicable. If a rationale is provided, the criteria is considered Present ("Yes"). An assessment of the rationale will be considered during the review of the application.				**Present**		**Not Present (No)**
					Yes	**N/A**	
		reports may not be necessary with respect to those requirements. Refer to 13(a).					
		a.	Sterilization		☐	☐	☐
		b.	Biological/Microbiological		☐	☐	☐
		c.	Immunological		☐	☐	☐
		d.	Toxicological/Biocompatibility		☐	☐	☐
		e.	Engineering (stress, wear, etc.)		☐	☐	☐
		f.	Chemistry/Analytical (typically for IVDs)		☐	☐	☐
		g.	Shelf Life		☐	☐	☐
		h.	Animal Studies		☐	☐	☐
		i.	Other Essential Laboratory Testing		☐	☐	☐
	10.	Is a summary of clinical experience and investigation(s) and results provided? [814.104(b)(4)(i) as applicable]			☐	☐	☐
		a.	Are the final versions of the clinical protocols included? (If performed under IDE, these should be the final FDA-approved versions of the clinical protocols, incorporating any Notices of Changes.)		☐		☐
		b.	Is a description of study population demographics provided?		☐		☐
		c.	Is a description of adverse events (e.g., adverse reactions, complaints, discontinuations, failures, replacements) provided?		☐		☐
		d.	Have report forms for patients who died or who did not complete the investigation been provided (i.e., to resolve potential bias)? Check "N/A" only if no patients died or were discontinued.		☐		☐
	11.	Are statistical analyses of the clinical investigations provided, if appropriate? [814.104(b)(4)(i)]			☐	☐	☐
		a.	Are the results of all analyses identified in the protocol provided?		☐		☐
	12.	Has appropriate draft labeling been submitted? [814.104(b)(4) and 814.20(b)(10)]					
		a.	Physician Labeling		☐		☐
			i.	Are indications for use included?	☐		☐
			ii.	Are contraindications, warnings, and precautions included?	☐		☐
			iii.	Are instructions for use included?	☐		☐
			iv.	Does the labeling include the statement: "Humanitarian Device. Authorized by Federal law for use in the [treatment or diagnosis] of [specify disease or condition]. The effectiveness of this device for this use has not been	☐		☐

Inventory of Organizational and Administrative Elements (Requirements per 21 CFR 814.112 unless otherwise indicated)							
Check "Yes" if item is present, "N/A" if it is not needed and "Not Present" if it is not included but needed.							
	• Any "Not Present" answer may result in a "Refuse to File" decision. • Each element on the checklist should be addressed within the application. An applicant may provide a rationale for omission for any criteria that are deemed not applicable. If a rationale is provided, the criteria is considered Present ("Yes"). An assessment of the rationale will be considered during the review of the application.				**Present**		**Not Present (No)**
					Yes	**N/A**	
				demonstrated" [814.104(b)(4)(ii)]			
		b.	Patient Labeling Check Check "N/A" only if the relevant lead Center has previously indicated that patient labeling is not necessary.		☐	☐	☐
		c.	Technical/Operators Manual, if applicable		☐	☐	☐
	13.	Statements/Certifications/Declarations of Conformity [814.104(b)(4), 814.20(b)(5), and 814.20(b)(12)]					
		a.	Has the applicant provided documentation to establish conformance with applicable performance standards and/or voluntary consensus standards? Check "N/A" only if no standards are used.		☐	☐	☐
		b.	Has the applicant provided documentation to establish that it has followed the recommendations in applicable FDA guidance or otherwise met applicable statutory or regulatory criteria? Check "N/A" only if no guidance is used.		☐	☐	☐
		c.	Investigator Financial Disclosure For additional information refer to the guidance document "Guidance for Industry – Financial Disclosure by Clinical Investigators" (https://www.fda.gov/RegulatoryInformation/Guidances/UCM341008) As required by 21 CFR Part 54, has the applicant submitted for each clinical investigator either: 1. A signed and dated Certification Form (3454) or 2. A signed and dated Disclosure Form (3455) Note: the signature should be from a responsible corporate official or representative of the applicant.		☐ ☐	☐ ☐	☐ ☐
			i.	For a Certification Form (3454): Is the required list of all investigators and subinvestigators attached to the Form?	☐	☐	☐
			ii.	If box 3 of Form 3454 is checked, does the Form include an attachment with the reason(s) why financial disclosure information could not be obtained?	☐	☐	☐
			iii.	For a Disclosure Form (3455): Does the application provide details of the financial arrangements and interests of the investigator(s) or subinvestigator(s), along with a description of any steps taken to minimize potential bias?	☐	☐	☐
		d.	Environmental Assessment under 21 CFR 25.20(n) [814.104(b)(4) and		☐		☐

Inventory of Organizational and Administrative Elements (Requirements per 21 CFR 814.112 unless otherwise indicated)								
Check "Yes" if item is present, "N/A" if it is not needed and "Not Present" if it is not included but needed.								
	• Any "Not Present" answer may result in a "Refuse to File" decision. • Each element on the checklist should be addressed within the application. An applicant may provide a rationale for omission for any criteria that are deemed not applicable. If a rationale is provided, the criteria is considered Present ("Yes"). An assessment of the rationale will be considered during the review of the application.						**Present**	**Not Present (No)**
							Yes / **N/A**	
			814.20(b)(11)]					
			i.	If claiming a categorical exclusion, information to justify the exclusion, OR			☐ ☐	☐
			ii.	An environmental assessment (ONLY required for devices that present new environmental concerns)			☐ ☐	☐
		e.	Did the application include a completed FORM FDA 3674, *Certification with Requirements of ClinicalTrials.gov Data Bank*? (42 U.S.C. 282(j)(5)(B) and 42 CFR part 11) Note: Enter the NCT number(s) in the Center Tracking System (CTS)				☐	☐
			Data from FORM FDA 3674 (mark "Yes" for the applicable one):					
			i.	No clinical trials referenced in application.			☐ ☐	
			ii.	Requirements are not applicable to referenced clinical trials.			☐ ☐	
			iii.	Requirements are applicable and have been met.			☐ ☐	
	14.	Pediatric Use - Per 515A(a)(2) of the FD&C Act, did the application include, if readily available: [814.104(b)(6) and 814.20(b)(13)]						
		a.	A description of any pediatric subpopulations that suffer from the disease or condition that the device is intended to treat, diagnose, or cure, or statement that no pediatric subpopulation exists for the disease or condition for which the device is intended. This statement does not mean the device is indicated for treating pediatric patients. For additional information refer to the guidance document "Providing Information about Pediatric Uses of Medical Devices - Guidance for Industry and Food and Drug Administration Staff" at https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM339465.pdf.				☐	☐
		b.	The number of affected pediatric patients.				☐	☐
B.	Issues Identified by FDA Prior to receipt of the HDE Application - history of the applicant with this device							
	1.	Does the applicant list prior applications or state that there were no prior applications? (may be located in CDRH Coversheet Form FDA 3514, Section F) If the applicant lists prior applications, address the applicable questions below:					☐	☐
		a.	510(k) #_____				☐ ☐	
			i.	If this device has been the subject of an NSE decision, have the data presented in the HDE taken into account any concerns related to safety or probable benefit that were previously communicated during the review of the prior 510(k) or through 510(k) correspondence?			☐ ☐	☐

Inventory of Organizational and Administrative Elements (Requirements per 21 CFR 814.112 unless otherwise indicated)								
Check "Yes" if item is present, "N/A" if it is not needed and "Not Present" if it is not included but needed.								
	• Any "Not Present" answer may result in a "Refuse to File" decision. • Each element on the checklist should be addressed within the application. An applicant may provide a rationale for omission for any criteria that are deemed not applicable. If a rationale is provided, the criteria is considered Present ("Yes"). An assessment of the rationale will be considered during the review of the application.					**Present**		**Not Present (No)**
						Yes	**N/A**	
		b.	IDE #_____			☐	☐	
			i.	Have the data presented in the HDE taken into account any safety or probable benefit concerns (e.g., "future considerations") previously communicated during the review of prior IDE(s) or through IDE correspondence?		☐	☐	☐
		c.	PMA #_____			☐	☐	
			i.	If a previously submitted PMA for this device has been withdrawn or denied, does the current HDE application take into account any issues related to safety or probable benefit raised during review of the prior PMA(s) or through PMA correspondence?		☐	☐	☐
		d.	HDE #_____			☐	☐	
			i.	If a previously submitted HDE application for this device has been withdrawn or denied, does the current HDE application take into account any issues related to safety or probable benefit raised during review of the prior HDE application or through HDE correspondence?		☐	☐	☐
		e.	Modular HDE #_____			☐	☐	
			i.	If "Yes", how many modules submitted? _____ How many modules were closed? _____				
			ii.	If there are modules that are on hold, does the HDE address outstanding deficiencies?		☐	☐	☐
	2.	Does the applicant list Pre-Submission(s) regarding the device or this application in which FDA feedback regarding data or information related to safety and/or probable benefit in the HDE was provided by email or during a meeting (in person or by phone), or state that there were no prior Pre-Submission interactions with the FDA regarding this application? If the applicant lists Pre-Submissions, address the applicable questions below:					☐	☐	☐
		a.	Pre-Submission #_____ Meeting date(s), if applicable_____					
		b.	Copy of minutes from each meeting or other written feedback?			☐	☐	☐
		c.	Were all FDA concerns or action items previously presented to the applicant in the Pre-Submission minutes or feedback addressed in the HDE or has the applicant provided a detailed scientific or clinical justification for an alternative approach?			☐	☐	☐

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Filing Decision Questions			
A "No" answer will typically result in a Not-Filed decision.			
		Yes	**No**
Decision 1	**Is the HDE complete?** **If, on its face, the HDE is missing one or more required elements (identified above), such that the application is not sufficiently complete to permit substantive review, answer "No."**	☐	☐
Decision 2	**From only an administrative review, does the HDE include information that appears to constitute valid scientific evidence?** **Only answer "No" if it is clear that the HDE is supported solely by information that 21 CFR 860.7 identifies as not constituting valid scientific evidence:** • **isolated case reports** • **random experience** • **reports lacking sufficient details to permit scientific evaluation** • **unsubstantiated opinions** **Comments:**	☐	☐
Decision 3	**Does the HDE address the key nonclinical and clinical issues identified by FDA prior to submission of the HDE application?** **OR** **Has the applicant provided a detailed scientific or clinical justification for the alternate approach?** Section B of the checklist outlines questions intended to identify when the FDA has previously provided specific guidance to the applicant about the content of the HDE application through one or more mechanisms, such as a prior HDE or PMA application, a prior "Not Substantially Equivalent" decision on a 510(k), Investigational Device Exemption (IDE) letters, feedback through the Q-submission Program, a Determination or Agreement meeting(s), or other substantive communication with FDA, or through a published guidance document. If such information has been communicated to the applicant through one or more of these mechanisms, and the HDE application addresses each of the key nonclinical and clinical issues identified by FDA, the answer to the above question is "Yes." Furthermore, if some of these key issues previously identified by FDA are not addressed, but the HDE application contains a scientific or clinical justification for the omission or deviation, the answer to the above question is "Yes." These cases do not preclude the responsible review Division from accepting the HDE application. In this context, the term "key issues" is meant to refer to issues that are central to FDA's review of the device's safety and probable benefit under sections 515 and 520(m) of the FD&C Act. Examples of key issues include: need for long-term nonclinical studies (e.g., biocompatibility, carcinogenicity, or other animal studies), and certain clinical study parameters (e.g., sample size, patient population, study design, and endpoints). These key issues are typically device-specific. As a result, the decision of FDA to "Refuse to File" an HDE application based on this criterion can only be made after carefully considering the following questions: *Are the types of necessary nonclinical and clinical studies well-known in the scientific and*	☐ ☐	☐ ☐

Filing Decision Questions			
A "No" answer will typically result in a Not-Filed decision.			
		Yes	**No**
	medical communities for the particular device? For an "established" device type, the types of nonclinical and clinical studies that we would expect in a PMA are likely to be well-known both within FDA and in the scientific and medical communities and, as such, are often included as part of an FDA guidance document and/or consensus standard. You should bear in mind that, for HDEs, the device may not be of an established device type. *Were the issues conveyed to the applicant as part of a documented regulatory process?* Examples of a documented regulatory process include: • interaction through the Q-submission process, • prior PMA or HDE application, • prior "Not Substantially Equivalent" decision on a 510(k), • IDE letters, or • letter(s) issued as a result of Determination or Agreement meetings. *Were the issues conveyed to the applicant related to insufficient effectiveness data?* Devices approved under an HDE application are exempt from the requirement to demonstrate a reasonable assurance of effectiveness. If an issue relates to insufficient effectiveness data, filing the HDE may be appropriate in cases for which accepting a PMA would not. FDA staff should only designate an HDE "Refuse to File" based on a "No" response to "Acceptance Decision 3" in instances where the key issues were identified by FDA staff as part of a documented regulatory process.		

Decision: FDA Staff Recommendation: File ___ Not File ___

Appendix B – Considerations for the Probable Benefit-Risk Assessment

As discussed in Section VI of this guidance, FDA considers the same factors described in FDA's benefit-risk framework for evaluating PMAs or De Novo requests when assessing probable benefits and risks for HDE applications. Refer to the FDA guidance document, "Factors to Consider when Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications," for a description of those factors. It should be clearly noted, however, that probable benefit and probable benefit-risk determinations under an HDE are different from those under a PMA or a De Novo request. Please refer to Sections V and VI of the guidance for further discussion related to these differences and the probable benefit-risk assessment. The tools identified in Appendices B and C are meant to serve complementary roles, and both should be completed as part of the probable benefit-risk assessment.

Instructions: FDA staff should make their recommendation regarding the probable benefit-risk assessment based on the totality of the evidence. The probable benefit-risk assessment is part of the decision whether to approve the application, but it does not include an assessment of all applicable requirements for approval. An indication from these tools that the probable benefits outweigh the risks does not mean that the application satisfies other applicable requirements for an HDE application.

The following questions are intended as a sequential method to help weigh various factors as part of the probable benefit-risk assessment. As such, the questions are intended to help identify and explain which factors and considerations are critical in making a probable-benefit risk assessment for a particular device. However, the questions are not intended to suggest that considerations other than those listed in the completed worksheet are irrelevant.

Consider questions 1-8 for Column A (the proposed Indications for Use), to help determine if the application is approvable for the proposed indications or, if narrowed indications for use are appropriate and can be agreed upon with the sponsor, consider questions 1-8 in Column B. However, as reflected under question 1, if the evidence does not support a finding of probable benefit under the proposed Indications for Use (or narrowed Indications for Use), or evidence does not support a finding of probable benefit for the proposed Indications for Use and agreement on narrowed Indications for Use is not achievable or applicable, the application would not be approvable.

Assessment of Probable Benefit

1. **Is there any evidence of clinical benefit?**

   Complete question 1a for therapeutics or invasive/implantable diagnostics; complete question 1b for other diagnostics.

   Note that in lieu of summaries, conclusions, and results of clinical investigations required under 21 CFR 814.20(b)(3)(v)(B), (b)(3)(vi), and (b)(6)(ii), HDE applicants are required to submit summaries, conclusions, and results of all clinical experience or investigations (whether adverse or

supportive) reasonably obtainable by the applicant that are relevant to an assessment of the risks and probable benefits of the device (see 21 CFR 814.104(b)(4)(i)).

a. Therapeutics or invasive/implantable diagnostics: Is a clinical benefit demonstrated for the device for this indication (e.g., from any one or more of the primary and/or secondary datasets or from associated real world evidence)? Probable benefit may be considered in terms of how a patient feels, functions, survives, or an acceptable surrogate outcome. Probable benefit may also be considered in terms of convenience in managing a disease or condition. *Select any of the following that demonstrate benefit.*

Indication

A	B	
☐	☐	A favorable change in at least 1 clinical assessment which is equal to or greater than seen in the control group
☐	☐	A favorable change in at least 1 clinical assessment which meets a predetermined performance goal
☐	☐	A favorable change in at least 1 clinical assessment which meets or surpasses a minimally important clinical difference
☐	☐	A favorable change in at least 1 clinical assessment which is equal to or greater than seen with other available modalities for the disease or condition
☐	☐	A favorable change in at least 1 clinical assessment which would be meaningful to patients considering the severity, chronicity, etc., of the condition, taking into consideration patient-reported outcomes and health-related quality of life
☐	☐	A favorable change in non-clinical data or modeling that is deemed to be predictive of clinical outcomes
☐	☐	Other(s) Click here to list other(s)

b. Other diagnostics: Is a clinical benefit demonstrated, based on accurate measurement of the diagnostic analyte(s)/biomarker in the indicated population? *Select one or more of the following clinical indications that demonstrate benefit, if applicable.*

Indication

A	B	
☐	☐	Disease susceptibility (likely future occurrence of a disease or condition)
☐	☐	Screening
☐	☐	Diagnosis
☐	☐	Prognosis
☐	☐	Monitoring
☐	☐	Treatment selection/modification
☐	☐	Other(s) Click here to list other(s)

Question 1: Is there any evidence of clinical benefit?

Indication

A	B	
☐	☐	YES → Continue to Question 2
☐	☐	NO → Move one column to the right or, if final column has been reached and you have determined there is no evidence of clinical benefit, do not approve the application.

2. What is the degree of uncertainty for the probable benefits?

a. Recognizing that some degree of uncertainty always exists, select the elements that contribute to uncertainty, if applicable, in the data regarding probable clinical benefit.

Indication

A	B	
☐	☐	Inconsistent or conflicting results between studies
☐	☐	Wide confidence intervals surrounding the point estimate(s) and/or odds ratio(s)
☐	☐	High subject loss-to-follow-up at critical assessment point(s)
☐	☐	Large amount of missing data at critical assessment time(s) +/- imputation
☐	☐	Significant number of major protocol deviations
☐	☐	Impact of confounding interventions
☐	☐	Inconsistent user experience or user experience not representative of likely real world user
☐	☐	Non-clinical data or modeling that does not adequately represent the clinical circumstance
☐	☐	Real World Evidence (RWE) is not relevant or reliable for the purposes of the proposed analysis
☐	☐	Inspectional findings
☐	☐	Study results are not generalizable to population under consideration
☐	☐	Other(s) Click here to list other(s)

b. Diagnostics: Select the performance characteristics that contribute to uncertainty for analytical validation of the device:

Indication

A	B	
☐	☐	Sensitivity
☐	☐	Specificity/Interference
☐	☐	Accuracy
☐	☐	Precision
☐	☐	Reproducibility
☐	☐	Reportable range or status
☐	☐	Linearity/Recovery
☐	☐	Matrix, carryover
☐	☐	Calibrators and/or controls
☐	☐	Pre-analytical
☐	☐	Post-analytical
☐	☐	Other(s) Click here to list other(s)

Question 2: What is the degree of uncertainty for the probable benefits?

Indication

A	B	
☐	☐	Low → Continue to Question 3; consider suggesting a different kind of marketing application.
☐	☐	Medium → Continue to Question 3
☐	☐	High → Continue to Question 3

Comments on the Assessment of Probable Benefit

For the Proposed Indications for Use (Column A):

Click here to enter summary of the Assessment of Probable Benefit for the proposed Indications for Use. Include a description of your assessment of the extent of probable benefit, considering the type, magnitude, and probability of benefit(s); and the duration of effects. Include a description of the impact of uncertainty on your Assessment of Probable Benefit.

For the narrowed Indications for Use (modified indication and/or population) (Column B):

Click here to enter summary of the Assessment of Probable Benefit for the narrowed Indications for Use. Include a description of your assessment of the extent of probable benefit, considering the type, magnitude, and probability of benefit(s); and the duration of effects. Include a description of the impact of uncertainty on your Assessment of Probable Benefit.

Assessment of Risk

3. Are known/probable risks more than minimal?

Select the elements that apply for known/probable risks that are more than minimal.

Indication

A	B	
☐	☐	Adverse events (AEs) or outcomes related to the device itself
☐	☐	AEs or outcomes related to the use of the device or procedure to use the device
☐	☐	AEs or outcomes related to anesthesia or sedation to use the device
☐	☐	AEs or outcomes due to subsequent tests/treatments needed (e.g., radiation from CT scans)
☐	☐	AEs or outcomes, not seen in the study/data, but probable based on "class effect" or events known to occur with similar technologies
☐	☐	False positive/false negative/absent result for diagnostics
☐	☐	Other(s) Click here to list other(s)

Question 3: Are known/probable risks more than minimal?

Indication

A	B	
☐	☐	YES → Continue to Question 4
☐	☐	NO → Continue to Question 4

4. What is the degree of uncertainty for the risks?

Recognizing that some degree of uncertainty always exists, select the elements that contribute to uncertainty, if applicable, in the data regarding the adverse events/outcomes or risks.

Indication

A	B	
☐	☐	Insufficient patient/subject numbers to detect serious events
☐	☐	Insufficient duration of follow-up to detect delayed/late events

A B
☐ ☐ Lack of data on repeated exposure to the device/use
☐ ☐ Inconsistent or conflicting results between studies
☐ ☐ Proper evaluations not performed as part of the study protocol to adequately detect certain AEs
☐ ☐ Poor or inconsistent adverse event definitions and documentation
☐ ☐ Events likely confounded by, and attributed to, other comorbidities or treatment modalities
☐ ☐ High subject loss-to-follow-up at critical assessment point(s)
☐ ☐ Large amount of missing data at critical assessment time(s) +/- imputation
☐ ☐ Significant number of major protocol deviations
☐ ☐ Inconsistent user experience or user experience not representative of likely real world user
☐ ☐ False positive/false negative/absent/indeterminate result for diagnostics
☐ ☐ Other(s) Click here to list other(s)

Question 4: What is the degree of uncertainty for the risks?

Indication

A B
☐ ☐ Low → Continue to Question 5
☐ ☐ Medium → Continue to Question 5
☐ ☐ High → Continue to Question 5

Comments on the Assessment of Risk
If you answered "No" to Question 3 but "High" to Question 4, please explain here.

For the Proposed Indications for Use (Column A):
Click here to enter summary of the Assessment of Risk for the proposed Indications for Use. Include a description of your assessment of the extent of probable risk considering the severity, types, number and rates of harmful events associated with use of the device; probability of a harmful event; duration of harmful events; and risk from false-positive or false-negative results for diagnostics. Include a description of the impact of uncertainty on your Assessment of Risk.

For the narrowed Indications for Use (modified indication and/or population) (Column B):
Click here to enter summary of the Assessment of Risk for the narrowed Indications for Use. Include a description of your assessment of the extent of probable risk, considering the severity, types, number and rates of harmful events associated with use of the device; probability of a harmful event; duration of harmful events; and risk from false-positive or false-negative results for diagnostics. Include a description of the impact of uncertainty on your Assessment of Risk.

Assessment of Probable Benefit-Risk

Provide a recommendation based on the totality of the evidence. As noted above, the probable benefit-risk assessment is part of the decision regarding whether to approve an HDE application but is not an assessment of all applicable requirements.

5. Do the Probable Benefits outweigh the Risks, considering the assessment of Probable Benefit and Risk and the degree of uncertainty identified above, and taking into account the

probable benefits and risks of currently available devices or alternative forms of treatment?

To approve an HDE application, FDA must find, among other things, that the device will not expose patients to an unreasonable or significant risk of illness or injury and that the probable benefit to health from the use of the device outweighs the risk of injury or illness from its use, taking into account the probable benefits and risks of currently available devices or alternative forms of treatment. Consider how the probable benefits and risks identified above compare to currently available devices or alternative forms of treatment and select the elements that apply:

Indication

A	B	
☐	☐	No legally marketed alternative medical product or medical intervention exists or the device offers advantages over other modalities
☐	☐	The device fills an unmet medical need or niche for more effective treatment or diagnosis of life-threatening or irreversibly debilitating human disease/conditions
☐	☐	The probable benefit of the device is equivalent to or greater than the probable benefits of other modalities
☐	☐	The probable risk of the device is no greater or is less than the probable risks of other modalities
☐	☐	The probable benefit of the device is less than the probable benefits of other modalities
☐	☐	The probable benefit of the device is less than the probable benefits of other modalities
☐	☐	The probable risk of the device is greater than the probable risks of other modalities
☐	☐	Other(s) Click here to list other(s)

Question 5: Do the Probable Benefits outweigh the Risks, considering the assessment of Probable Benefit and Risk and the degree of uncertainty identified above, and taking into account the probable benefits and risks of currently available devices or alternative forms of treatment?

Indication

A	B	
☐	☐	Yes – The probable benefits outweigh the risks such that, for this device, additional consideration of relevant factors would not change that determination.
☐	☐	Undetermined – The probable benefits may not outweigh the risks, and further discussion and consideration of relevant factors is appropriate → Move to Question 6

Comments on Assessment of Probable Benefit-Risk

For the Proposed Indications for Use (Column A):

Click here to summarize the probable benefit(s) that have been demonstrated for the proposed Indications for Use and your assessment of how Probable Benefit(s) compare to Risks. Include a description of how available alternative modalities, including their probable benefits and risks, affect your assessment. Include a description of how uncertainty regarding Probable Benefit(s) and Risks affects your assessment.

For the narrowed Indications for Use (modified indication and/or population) (Column B):

Click here to summarize the probable benefit(s) that have been demonstrated for the narrowed Indications for Use and your assessment of how the Probable Benefit(s) compare to Risks. Include a description of how available alternative modalities, including their probable benefits and risks, affect your assessment. Include a description of how uncertainty regarding Probable Benefit(s) and Risks affects your assessment.

6. Do the Probable Benefits outweigh the Risks, when taking into account additional relevant considerations? *Select relevant considerations.*

Indication

A	B	
☐	☐	Available patient preference information (PPI) showing patients willingness or unwillingness to accept the probable risks in exchange for the probable benefits
☐	☐	Available qualitative or quantitative PPI on the relative desirability or acceptability to patients of outcomes or other attributes that differ among alternative health interventions
☐	☐	Understanding that the device represents novel technology for which the current device technology is different
☐	☐	Ability to manage the condition and consideration of natural history of disease progression in the absence of the intervention with the device under review
☐	☐	The adverse events associated with use of the device are reversible
☐	☐	Type of intervention required to address the harmful event (e.g., medication, surgery)
☐	☐	Understanding of mechanistic plausibility and/or "class effect" (e.g., familiarity with similar technology)
☐	☐	Other(s) Click here to list other(s)

Question 6: Do the Probable Benefits outweigh the Risks, when taking into account additional relevant considerations?

Indication

A	B	
☐	☐	Yes –The probable benefits outweigh the risks such that, for this device, additional consideration of relevant factors would not change that determination.
☐	☐	Undetermined – The probable benefits may not outweigh the risks, and discussion and consideration of risk mitigation measures is appropriate → Move to Question 7

Comments on Assessment of Probable Benefit-Risk, taking into account additional relevant considerations

For the Proposed Indications for Use (Column A):

Click here to summarize the probable benefit(s) that have been demonstrated for the proposed Indications for Use and your assessment of how Probable Benefit(s) compare to Risks. Include a description of how available alternative modalities, including their probable benefits and risks, affect your assessment. Include a description of how uncertainty regarding Probable Benefit(s) and Risks affects your assessment. Include a description of how patient perspectives affected your assessment.

For the narrowed Indications for Use (modified indication and/or population) (Column B):

Click here to summarize the probable benefit(s) that have been demonstrated for the narrowed Indications for Use and your assessment of how Probable Benefit(s) compare to Risks. Include a description of how available alternative modalities, including their probable benefits and risks, affect your assessment. Include a description of how uncertainty regarding Probable Benefit(s) and Risks affects your assessment. Include a description of how patient perspectives affected your assessment.

7. Can the risks be mitigated, so that Probable Benefits outweigh the Risks? Consider if the Probable Benefits outweigh the Risks if risk mitigation strategies are incorporated to lower the probability of a harmful event occurring and improve the probable benefit-risk profile of the device. *Select relevant considerations:*

Indication

A	B	
☐	☐	Additional descriptions of known and probable benefits and risks in physician and patient labeling, including adequate Contraindications, Warnings, and Precautions and description of the clinical events
☐	☐	Additional warnings noting limitations of safety information (e.g., "The safety of the use of this device in [situation] has not been evaluated.")
☐	☐	Labeling the device for prescription use only
☐	☐	Limitation to caregivers with certain qualifications or clinical training
☐	☐	Limit to users with a minimum set of qualifications and/or training
☐	☐	Physician/user training program
☐	☐	Device tracking
☐	☐	Other(s) Click here to list other(s)

Question 7: Can the risks be mitigated, so that Probable Benefits outweigh the Risks?

Indication

A	B	
☐	☐	Yes –The probable benefits outweigh the risks such that, for this device, additional consideration of relevant factors would not change the determination.
☐	☐	Undetermined – The probable benefits may not outweigh the risks, and further discussion and consideration of postmarket actions is appropriate → Move to Question 8

Comments on Assessment of Probable Benefit-Risk, considering risk mitigation strategies

For the Proposed Indications for Use (Column A):

Click here to summarize the probable benefit(s) that have been demonstrated for the proposed Indications for Use and your assessment of how Probable Benefit(s) compare to Risks. Include a description of how available alternative modalities, including their probable benefits and risks, affect your assessment. Include a description of how uncertainty regarding Probable Benefit(s) and Risks affects your assessment. Include a description of how patient perspectives affected your assessment.

For the narrowed Indications for Use (modified indication and/or population) (Column B):

Click here to summarize the probable benefit(s) that have been demonstrated for the narrowed Indications for Use and your assessment of how Probable Benefit(s) compare to Risks. Include a description of how available alternative modalities, including their probable benefits and risks, affect your assessment. Include a description of how uncertainty regarding Probable Benefit(s) and Risks affects your assessment. Include a description of how patient perspectives affected your assessment.

8. Do the Probable Benefits outweigh the Risks considering the use of postmarket actions? *Select appropriate postmarket action(s).*

Indication

A B
☐ ☐ Collection of additional and/or confirmatory non-clinical performance data in the postmarket space
☐ ☐ Collection of additional and/or confirmatory clinical data in the postmarket space
☐ ☐ Other(s) Click here to list other(s)

Question 8: Do the Probable Benefits outweigh the Risks considering the use of postmarket actions?

Indication

A B
☐ ☐ Yes – The probable benefits outweigh the risks.
☐ ☐ No – If you have determined that the probable benefits do not outweigh the risks, move to the right column in the table to assess the probable benefits and risks for a narrowed indication, or if the final column has been reached, and you have determined that the probable benefits do not outweigh the risks, do not approve the application.

Comments on the Assessment of Probable Benefit-Risk, considering postmarket actions

For the Proposed Indications for Use (Column A):

Click here to summarize the probable benefits(s) that have been demonstrated for the proposed Indications for Use and your assessment of how Probable Benefit(s) compare to Risks. Include a description of how available alternative modalities, including their probable benefits and risks, affect your assessment. Include a description of how uncertainty regarding Probable Benefit(s) and Risks affects your assessment. Include a description of how patient perspectives affected your assessment.

For narrowed Indications for Use (modified indication and/or population) (Column B):

Click here to summarize the probable benefits(s) that have been demonstrated for the narrowed Indications for Use and your assessment of how Probable Benefit(s) compare to Risks. Include a description of how available alternative modalities, including their probable benefits and risks, affect your assessment. Include a description of how uncertainty regarding Probable Benefit(s) and Risks affects your assessment. Include a description of how patient perspectives affected your assessment.

Appendix C – Probable Benefit-Risk Assessment Tool

HDE Probable Benefit-Risk Assessment: Decision Support Tool HDE Questions Based on the totality of the data	**A. Proposed Indications for Use**	**B. Potential Narrowing of Indications for Use**[1] Click here to insert modified Indications for Use, including those that do not get to "yes." Is the narrowed indication clinically reasonable?
Assessment of Probable Benefit	Considering benefit in terms of • Type • Magnitude • Probability • Duration of effects	Considering benefit in terms of • Type • Magnitude • Probability • Duration of effects
1. Is there any evidence of clinical benefit?	☐ YES → Q2 ☐ NO → move to B	☐ YES → Q2 ☐ NO → Not approvable
2. What is the degree of uncertainty for the Benefits?[2]	☐ High ☐ Medium ☐Low Continue to Q3	☐ High ☐ Medium ☐Low Continue to Q3
Assessment of Risk	Considering risk in terms of • Severity, types, number and rates of harmful events • Probability of a harmful event • Duration of harmful events • Risks from false-positive or false-negative results	Considering risk in terms of • Severity, types, number and rates of harmful events • Probability of a harmful event • Duration of harmful events • Risks from false-positive or false-negative results
3. Are known/probable risks more than minimal?	☐ YES → Q4 ☐ NO → Q4	☐ YES → Q4 ☐ NO → Q4
4. What is the degree of uncertainty for the Risks?	☐ High ☐ Med ☐Low Continue to Q5	☐ High ☐ Med ☐Low Continue to Q5
Assessment of Probable Benefit-Risk		
5. Do the Probable Benefits outweigh the Risks?[3]	☐ YES → Worksheet complete ☐ Undetermined → Q6	☐ YES → Worksheet complete ☐ Undetermined → Q6
6. Do the Probable Benefits outweigh the Risks, taking into account additional relevant considerations?	☐ YES → Worksheet complete ☐ Undetermined → Q7	☐ YES → Worksheet complete ☐ Undetermined → Q7
7. Can the risks be mitigated, so that Probable Benefits outweigh the Risks?	☐ YES → Worksheet complete ☐ Undetermined→ Q8	☐ YES → Worksheet complete ☐ Undetermined → Q8
8. Do the Probable Benefits outweigh the Risks considering the use of postmarket actions?	☐ YES → Worksheet complete ☐ NO → move to B	☐ YES → Worksheet complete ☐ NO → Not approvable

[1] Instructions: The term "indications for use" describes the disease or condition that the device will diagnose, treat, prevent, cure, or mitigate, including a description of the patient population for which the device is intended. See 21 CFR 814.20(b)(3)(i) and 814.104(b)(4). Consider the probable benefits and risks for a modified population for the proposed use, a modified indication for the proposed population, or both a modified indication and modified population, which would translate into a 'narrowing' of the Indications for Use from what was originally proposed. Note that probable benefit and probable benefit-risk determinations for HDEs are different from those under PMAs. For more information, refer to Section VI of this guidance when it is finalized.

[2] Instructions: If the degree of uncertainty is low, then consider whether a different kind of marketing application would be appropriate. However, low uncertainty does not necessarily imply clinically meaningful benefit.

[3] Instructions: For an HDE, take into account the probable benefits and risks of currently available devices or alternative forms of treatment.