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# Humanitarian Device Exemption (HDE) Program - Final Guidance

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# Agenda

- Definitions/Objectives
- Background of HDE program
- Scope of Guidance
- HDE Application Content, Review, and Timelines
- Post Approval Requirements
- Special Considerations for HDEs
- Summary/Significant Changes in HDE Guidance
- Resources
- Questions

# Definitions

- ***Humanitarian Use Device (HUD)***: A medical device 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.
- ***Humanitarian Device Exemption (HDE)***: A marketing application for a HUD, exempt from effectiveness requirements and subject to certain profit and use restrictions.
- ***Institutional Review Board (IRB)***: A committee that oversees the use of HUDs at medical facilities, per FDA regulations governing IRBs.
- ***Appropriate Local Committee (ALC)***: A standing committee that has expertise and experience in reviewing and making treatment decisions for clinical care.

# Objectives

- Provide an overview of the scope of the HDE program described in the FDA's Guidance Document [Humanitarian Device Exemption \(HDE\) Program : Guidance for Industry and Food and Drug Administration Staff](#) issued September 6, 2019
- Review significant changes made in the final guidance document
  - Final guidance supersedes *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.

# Evolution of the HDE Program

1990

- *Safe Medical Devices Act*
- Exemption from requirement to demonstrate reasonable assurance of effectiveness (Sections 514 and 515 of the FD&C Act)

1997

- *Food and Drug Administration Modernization Act (FDAMA)*
- Allowed use of HUDs under HDEs without prior IRB approval in certain emergency situations

2007

- *Food and Drug Administration Amendments Act (FDAAA)*
- Allowed HUDs indicated for use in pediatric patients, or a pediatric subpopulation, to be sold for profit

2012

- *Food and Drug Administration Safety and Innovation Act (FDASIA)*
- Further expanded the eligibility of devices able to make a profit



# 21<sup>st</sup> Century Cures Act

- 21<sup>st</sup> Century Cures Act (“Cures Act”) - effective 12/13/2016
  - Modified the HUD threshold to “not more than 8,000 individuals in the United States per year”
  - Revised requirement for approval of the use of HUDs at medical facilities
  - HDE Commitment: Publish draft guidance within 18 months to define the criteria for establishing “probable benefit” – published 6/30/2018
  - Current guidance represents finalization of this draft guidance and responses to public comments.

# Scope of Guidance Document

- Operational aspects of HDE Program
- Principal criteria that the FDA uses to determine probable benefit
- FDA's assessment of whether probable benefit outweighs the risk of injury or illness from its use
- Post-Approval requirements for HDEs
- Special Considerations for HDEs
- Decision tools for FDA staff when reviewing HDE applications

# HDE Application Content

- HUD Designation should be submitted to and approved by Office of Orphan Products prior to HDE submission
  - Guidance Document [Humanitarian Use Device \(HUD\) Designations - Guidance for Industry and Food and Drug Administration Staff](#), revised September 5, 2019
- HDE Filing review: Application should be organized and administratively complete (21 CFR 814.104(b))
  - Appendix A of the guidance
  - Applicant should provide a justification for any alternative approach
  - Filing decision made within 30 days from the date the HDE was received.

# HDE Application Content cont'd

- Reviewer may use discretion to use interactive review to obtain missing information during filing review or substantive review
- Device description:
  - all components and accessories and their mode of action
  - design drawings and specifications
  - materials
- Indications for Use
  - consistent with HUD designated disease or condition

# HDE Application Content cont'd

- Valid Scientific Evidence to demonstrate safety and probable benefit of the device
  - may include bench, animal, and/or clinical
    - principles of the “3Rs”: reduce, refine, and replace animal use in testing when feasible
  - guidance encourages collection and submission of patient preference information
- Explanation of why probable benefit outweighs risk
- Manufacturing Information – in accordance with Quality System Regulation (21 CFR 820)
- Labeling
  - physician
  - patient, if applicable

# HDE Filing

Elements unique to HDE filing include:

- HUD designation
  - Copy of or reference to FDA's HUD designation letter
- Amount to be charged for device
  - If more than \$250, a report must be provided verifying that the amount charged does not exceed the costs of research, development, fabrication, and distribution.
  - Should still include if eligible for profit-making
- Comparable devices
  - Statement that no other comparable device, other than a HUD approved under HDE or for use under an approved clinical investigation, is available to treat or diagnose the disease or condition



# HDE Review - Safety

- Substantive review of HDE Application must demonstrate:
  - the device will not expose patients to an unreasonable or significant risk of illness or injury AND
  - the probable benefit to health from use of the device outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment

# HDE Review – Probable Benefit

- When there is evidence for FDA to reasonably conclude that patients are likely to benefit from the use of the device, 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);
  - Patient perspectives; and/or
  - Care-partner (e.g., parent or aide) perspectives.

# HDE Review – Probable Benefit cont'd

- Reviewer's determination of "probable benefit" under an HDE:
  - Accepts greater uncertainty, as a reasonable assurance of effectiveness is not required
  - Considers intended use of the device, including target patient population and size of population
    - Ex: the smaller the patient population, the greater the uncertainty FDA would expect
  - Takes into account currently available alternative treatments or diagnostics
  - Takes into account patient perspectives on risk, uncertainty, and probable benefit

Guidance: *Consideration of Uncertainty in Making Benefit-Risk Determinations*, <https://www.fda.gov/media/115672/download>

# Timeline of HDE Actions

- FDA actions made within 75 days of receipt:
  - Approval order;
  - Approvable letter;
  - Major deficiency letter;
  - Not approvable letter; and
  - Denial order
- Major amendments will extend review time up to 75 days
- Voluntary withdrawal
  - Failure to respond within 75 days, unless extension is requested
  - Extensions granted up to 360 days

# Post Approval Requirements - IRB

- An IRB must provide oversight at facilities where HUDs are used
- Statutory language allows either an IRB or “an appropriate local committee” to approve the use of a HUD to treat or diagnose patients at a facility.
  - “Appropriate local committee” may include a standing committee at the facility that includes physicians with experience in the treatment of rare diseases or conditions
  - Approval for individual HUD use not required; a generalized approval may be granted for the facility.
  - Emergency use does not require prior approval

# Appropriate Local Committee (ALC)

- Has expertise and experience in reviewing and making treatment decisions for clinical care, particularly in applying innovative medical device technologies to clinical care.
- Includes physicians with experience in the treatment of rare diseases or conditions
- Examples may include:
  - Peer Review Committee
  - Credentialing Committee
  - Quality Care Committee

# IRB / ALC Review of HUD use

- For initial review, FDA *recommends* review of:
  - 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 ALC or by facility policy
  - 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

# Post Approval Requirements- Adverse Events

- All adverse events, whether expected or not, must be reported and evaluated in accordance with Medical Device Reporting requirements in 21 CFR part 803.
  - Device manufacturers and user facilities submit to FDA and IRB/ALC
  - Adverse events for HUDs that are approved and labeled for pediatric patients or in a pediatric subpopulation, and exempt from the profit prohibition, will be reviewed periodically by FDA's Pediatric Advisory Committee (PAC)

# Post approval- additional FDA submissions

- HDE supplements – 21 CFR 814.108
  - Supplements may follow review guidelines for PMAs, with some changes to review timelines.
  - A request for new indications should be accompanied by a new HUD designation
- Periodic Reports - 21 CFR 814.126
  - Updated information to demonstrate that the HUD designation is still valid
  - Updated explanation of why the device would otherwise not be available

# Post Approval Study

- May be required as a Condition of Approval in order to:
  - Understand long-term performance
  - Evaluate learning curve or training issues
- Full protocol/protocol outline, including relevant timepoints, is agreed upon prior to HDE approval
  - If only a protocol outline is agreed upon, a full protocol is developed following approval, in a protocol supplement to the HDE
- Recommendations included in the guidance document [\*Procedures for Handling Post-Approval Studies Imposed by PMA Order\*](#)

# Special HDE Considerations - Profit

- 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) unless:
  - Intended and labeled only for pediatric patients or in a pediatric subpopulation,
  - Disease does not occur in any pediatric populations or pediatric subgroups
  - Disease or condition occurs in pediatric patients in such numbers that the development of the device for such patients is impossible, highly impracticable, or unsafe.
- Applicant should provide adequate supporting documentation in the HDE

# Special HDE Considerations - ADN

- If eligible, a HUD can be sold for a profit up until the number of devices sold exceeds the annual distribution number (ADN).
- The applicant should provide the number of devices per year reasonably needed for each individual in the HDE application/supplement and provide adequate documentation to support such number.
- The ADN will be equal to or greater than 8,000, depending on how many devices per year are reasonably needed to treat diagnose, or cure an individual
- Once 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

# Special HDE Considerations – Information to Patients

- Informed consent not required from patient treated or diagnosed with an HDE-approved HUD
  - IRB or ALC may choose to require additional information be provided to patients
  - Written documents provided to patients should include much of the information provided in the HDE patient labeling
- Labeling must:
  - Be truthful and non-misleading
  - 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 demonstrated” as required in 21 CFR 814.104.

# Special HDE Considerations - Pediatrics

- Patients who are 21 years of age or younger (i.e., up to, but not including, the 22<sup>nd</sup> birthday) at the time of the diagnosis or treatment (Section 520(m) of the FD&C Act)
- HUDs labeled for use in pediatric patients or in a pediatric subpopulation may be eligible to be sold for profit
- HDE applications for devices intended for use in both pediatric and 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.

# Special HDE Considerations - Pediatrics

- Approved HUDs are required to be reviewed annually by the FDA Pediatric Advisory Committee (PAC)
  - Ensures that the HDE remains appropriate for the pediatric populations for which it was approved.
  - Conducts periodic review of adverse events for these devices when they are exempt from the profit prohibition

For more information on the PAC, see <https://www.fda.gov/advisory-committees/committees-and-meeting-materials/pediatric-advisory-committee>

# HDE Reviewer Tools – Filing Checklist

- Incorporated filing checklist into guidance (Appendix A)
  - Checklist helps to ensure that the application contains the necessary information to conduct a substantive review.
  - Elements in the checklist stem from either statutory or regulatory requirements
  - Format and content are consistent with the analogous checklists for other types of premarket submissions.
  - Concerns identified by the Agency regarding results and outcomes of nonclinical and clinical studies should be addressed in the substantive review and should not preclude a filing decision.

# HDE Reviewer Tools – Assessment of Probable Benefit and Risk

- Considerations for the Probable Benefit-Risk Assessment & Probable Benefit-Risk Assessment Summary (Appendices B & C)
  - Worksheets provide flexibility and use of scientific judgment in assessing the totality of the evidence to determine if a specific device meets the standard for HDE approval.
  - Allow 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
  - Prompt reviewers to consider specific criteria for
    - Probable benefit
    - Risk
    - Sources of uncertainty

# Summary

- Per the Cures Act, a HUD is defined as a device for use in a patient population that does not exceed 8,000 patients per year.
- Criteria provided for:
  - Determining probable benefit
  - Assessing whether the probable benefit outweighs the risk of use
- Allows for use of “appropriate local committees” in addition to IRBs to approve HUD use at facilities
- Provides reviewer tools to ensure consistency, as well as flexibility, in reviewer decision-making.

# Resources

- [Humanitarian Device Exemption \(HDE\) Program : Guidance for Industry and Food and Drug Administration Staff](#)
- [Humanitarian Use Device \(HUD\) Designations - Guidance for Industry and Food and Drug Administration Staff](#)
- [Modifications to Devices Subject to Premarket Approval \(PMA\) - The PMA Supplement Decision-Making Process](#)
- [30-Day Notices, 135-Day Premarket Approval \(PMA\) Supplements and 75-Day Humanitarian Device Exemption \(HDE\) Supplements for Manufacturing Method or Process Changes](#)
- [Procedures for Handling Post-Approval Studies Imposed by PMA Order](#)
- [Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications](#)
- [Consideration of Uncertainty in Making Benefit-Risk Determinations in Medical Device Premarket Approvals, De Novo Classifications, and Humanitarian Device Exemptions](#)
- [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](#)
- [eCopy Program for Medical Device Submissions](#)

# Questions?

Division of Industry and Consumer Education: [DICE@fda.hhs.gov](mailto:DICE@fda.hhs.gov)

Office of Regulatory Programs, Division 1: Division of Submission Support: [CDRHPremarketProgramOperations@fda.hhs.gov](mailto:CDRHPremarketProgramOperations@fda.hhs.gov)

Slide Presentation, Transcript and Webinar Recording will be available at:

<http://www.fda.gov/training/cdrhlearn>

Under Heading: How to Study and Market Your Device; Sub-Heading:  
HUD/HDE

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