



**U.S. Food and Drug Administration**  
Protecting and Promoting Public Health



# Humanitarian Device Exemption (HDE): Overview and Pre-approval Activities

**Donna Headlee, RN, BSN, CCRP**

Branch Chief, Premarket Programs Branch  
Division of Industry and Consumer Education  
Office of Communication and Education  
Center for Devices and Radiological Health  
U.S. Food and Drug Administration



# Learning Objectives

- Define Humanitarian Device Exemption (HDE) and Humanitarian Use Device (HUD)
- Describe the approval threshold: determination of reasonable safety and probable benefit
- Identify the contents of an HDE application
- Describe the HDE review process

# Learning Objectives

- Understand the different types of actions for an HDE
- Describe the contents of an HDE approval package
- Identify strategies/best practices for a successful HDE submission and review process

# Rationale for HDE Program

- Rare diseases or conditions occur in a small number of patients
- Challenges:
  - to treat or diagnose the disease or condition
  - to gather valid scientific evidence to support safety and effectiveness
- Safe Medical Devices Act of 1990
- Alternative regulatory pathway for medical devices to treat/diagnose rare diseases or conditions

# What is a Humanitarian Use Device (HUD)?

- A medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in not more than 8,000 individuals in the United States per year.

**Defined by 21 CFR 814.3(n) and  
Updated by Section 3052 of 21<sup>st</sup> Century Cures Act**

# What is a Humanitarian Device Exemption (HDE)?

- A marketing application for a HUD
- Exempt from the effectiveness requirements of Sections 514 and 515 of the FD&C Act
- Subject to certain profit and use restrictions

**Section 520(m) of FD&C Act**

# Two-Step Process

- **Step 1:** Obtain designation of the device as a HUD from the FDA's Office of Orphan Products Development (OOPD).
- **Step 2:** After HUD designation is granted, submit an HDE application to the Center for Devices and Radiological Health (CDRH) or Center for Biologics Evaluation and Research (CBER).

# Eligibility for HDE

1. Received HUD designation

**AND**

2. No legally marketed device for same disease or condition granted under:

- Premarket notification (510(k))
- Premarket approval (PMA)
- *de novo*



# Approval Threshold

## Reasonable Assurance Safety

And

## Probable Benefit\*



\*Exempt from requirement to establish reasonable assurance of effectiveness

# Basis to Approve HDE

- device use (**benefit**) outweighs risk of injury/illness (**safety**)
- accounting for other available options:
  - currently available devices or alternative forms of treatment
  - their respective benefits and risks



# Contents of HDE Application

# HDE Application - Contents

- Copy of/reference to HUD designation letter
- Explanation of why device not otherwise available
- Statement that no comparable device is legally marketed (approved or cleared)
- Device description:
  - all components and accessories and how they work
  - design drawings and specifications
  - materials

# HDE Application - Contents

- Indications for Use
  - consistent with HUD designated disease or condition
- Valid Scientific Evidence
  - may include bench, animal, and/or clinical
- Explanation of why probable benefit outweighs risk

# HDE Application - Contents

- Manufacturing Information
  - must comply with the Quality System Regulation (**21 CFR 820**)
- Amount being charged
- Request for Profit
  - if requesting exception to profit prohibition
- Labeling
  - physician
  - patient, if applicable

# Required Labeling Statements

- The device is a humanitarian use device and
- Although the device is authorized by Federal Law, the effectiveness of the device for the specific indication has not been demonstrated

# Clinical Evidence

- Sources:
  - clinical studies subject to Investigational Device Exemptions (IDEs) [i.e., conducted in United States]
  - outside of United States (OUS) experience
  - literature analyses
  - whether adverse or supportive



# Clinical Evidence

- **Evidence should include:**
  - summaries,
  - conclusions, and
  - results of **all** clinical experience or investigations
- Generally includes information on both safety and probable benefit

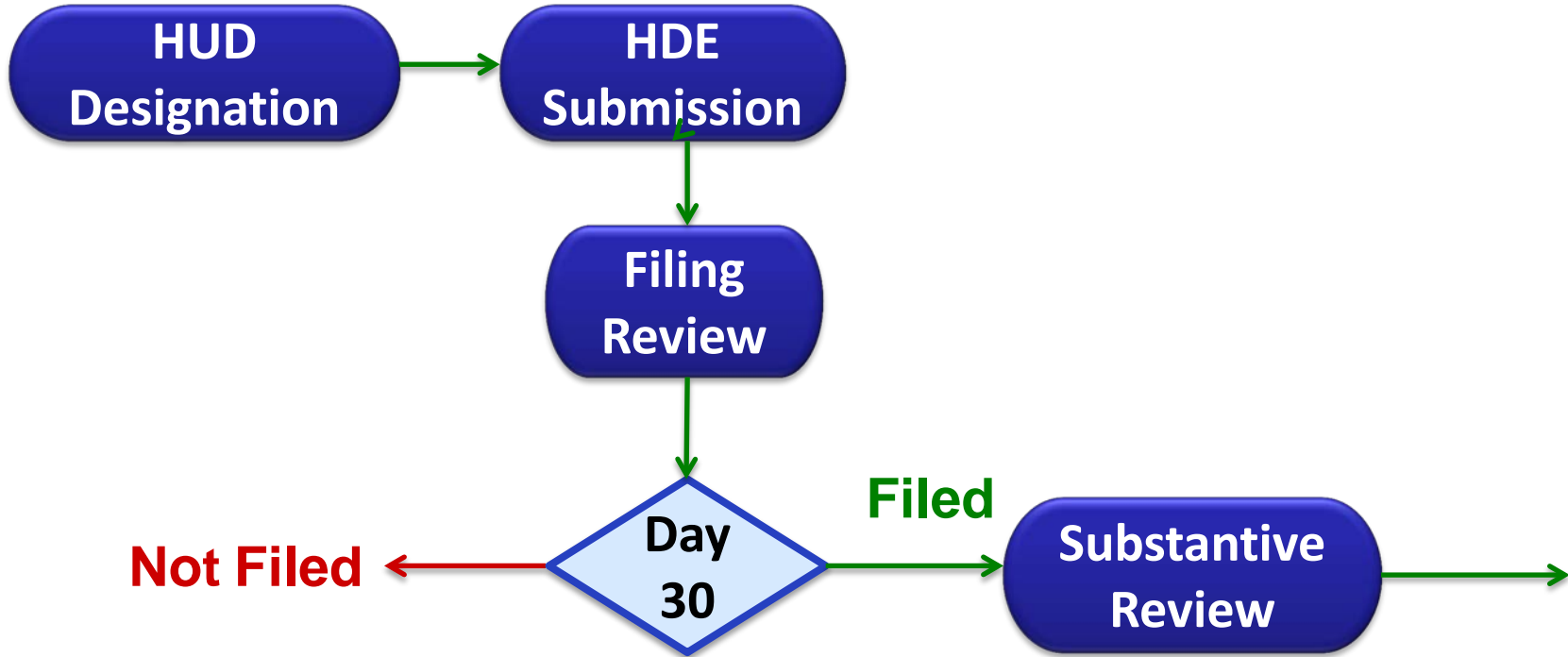
# Limitations of Clinical Evidence

- **Rare disease/condition:**
  - Limited patient population available to study
  - smaller sample sizes
- **Lack of available comparable device**
  - no active control arm
  - no randomization

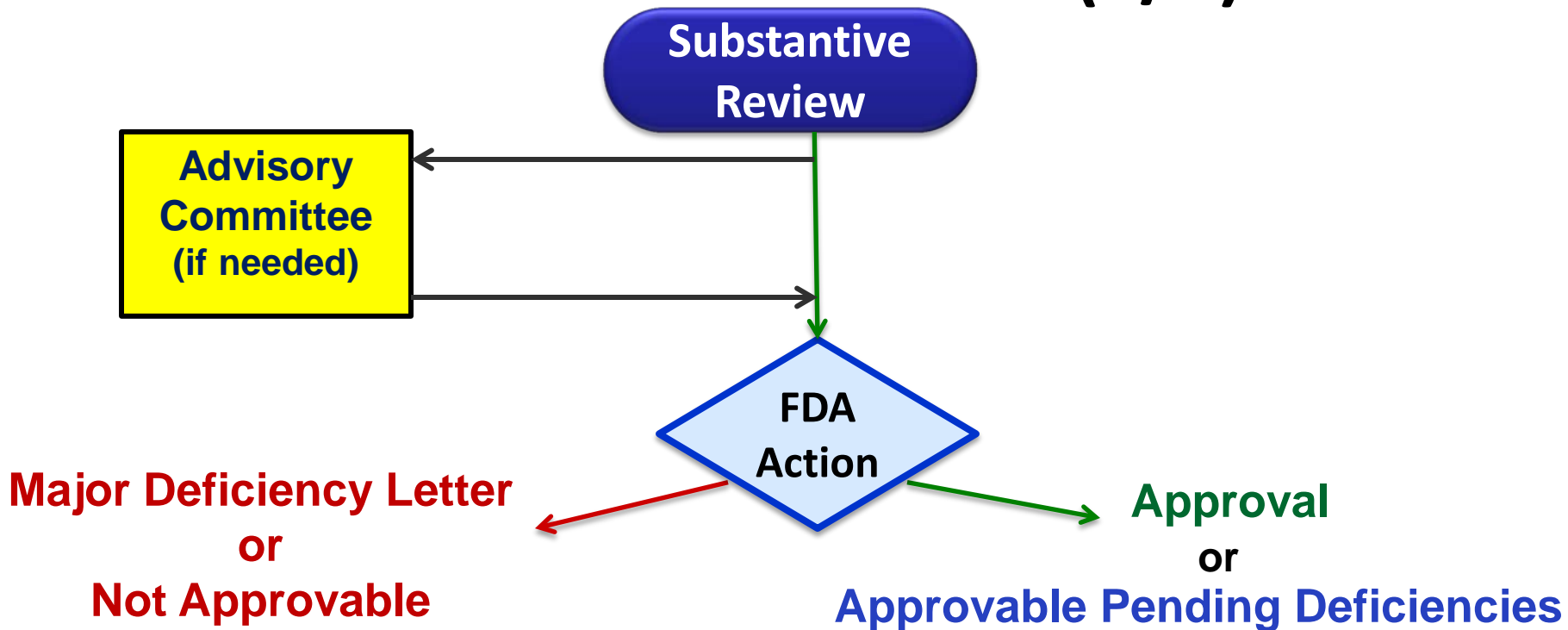


# HDE Review Process

# HDE Review Process (1/2)



# HDE Review Process (2/2)



# Multi-Disciplinary FDA Review Team

## Scientific, Regulatory, Quality System Review

- **Team Leader/Lead Reviewer**
- **Non-Clinical**
  - engineering
  - sterility, stability and shelf life
  - bench testing
  - biocompatibility
  - microbiology
  - animal studies
- **Clinical**
  - statistical
  - medical
  - epidemiology
  - labeling
- **Compliance**
  - quality systems and manufacturing
  - bioresearch monitoring

# Filing Review

- **Purpose**
  - threshold determination that the application is sufficiently complete to permit substantive review
- **FDA Action:**
  - FDA sends Applicant written notification of filing review
  - Decision Options: Filed or Not Filed
  - completed within **30 calendar days** of FDA receipt of HDE

# Reasons for Not Filing

- **Incomplete**
  - all the information required **(21 CFR 814.104(b))**
  - a statement of either certification or disclosure, or both **(21 CFR Part 54)**
- **FDA determines that there is a comparable device available**
- **Contains an untrue statement or omits material information**



# Substantive Review

- **Purpose**
  - Scientific, Regulatory and Quality Systems review
- **Interactive Process between FDA and Applicant**
  - address deficiencies that can be addressed in an appropriate timeframe
  - allows review to continue and meet the review milestones
  - FDA Review Clock does not stop

# Advisory Committee Meeting

- **Independent panel of experts**
  - expert clinicians
  - statisticians
  - industry representative
  - patient representative

# Advisory Committee Meeting

- FDA may seek input from Advisory Committee for reasons such as:
  - **novel technology** expected to have a **significant impact on clinical practice**
  - study results provide **significant uncertainty** as to whether the probable benefit of the device outweigh its probable risk
  - unanticipated **serious safety concerns**
  - significant study **data quality** or **data integrity** issues

# Advisory Committee Meeting

- **Provide recommendations:**
  - safety and probable benefit
  - benefits outweigh the risks
  - conditions of approval
  - labeling



# FDA Actions

# FDA Actions

- **Approval Order:**
  - Device may be marketed
  - identifies conditions of approval
- **Approvable Pending Deficiencies Letter:**
  - Device is not legally marketed
  - identify clarifications/deficiencies that need to be addressed to make HDE application approvable
  - Common reasons: unresolved labeling; unresolved post-approval study design; and/or FDA has not determined that the manufacturing facilities, methods and controls are in compliance with the Quality System Regulation

# FDA Actions

- **Major Deficiency Letter:**

- device is not legally marketed
- identifies deficiencies that cannot be adequately resolved interactively

- **Not Approvable Letter:**

- device is not legally marketed
- identify deficiencies that need to be addressed to make the HDE application approvable
- collection of new clinical/preclinical evidence



# Approval of an HDE



# HDE Approval Package

Once a HDE is approved, FDA makes these documents publically available:

- **Approval Order**
- **Summary of Safety and Probable Benefit (SSPB)**
- **Labeling**
  - professional labeling
  - patient labeling (if applicable)
- **Consumer Information**
  - a short, plain-language summary of the device and its intended use

# HDE Approval Order

- **HDE Approval Order**
  - HDE and HUD numbers
  - conditions of approval
  - post-approval requirement
  - specific items that may be identified on case-by-case basis
    - Annual Distribution Number (ADN), if applicable
    - specific reporting requirements
    - post-approval studies

# Conditions of Approval

- Approved labeling
- Post-approval record-keeping requirements
- HDE supplements for changes

# Conditions of Approval

- **Mandatory Reporting**
  - periodic (annual)
  - medical device reports (MDRs) and product recalls
- **Post-approval studies**
- **Updates to clinicians**

# Post-Approval Studies (PAS)

- **May be required as a condition of approval**
- **Reasons/Examples why FDA may require a PAS:**
  - understand long-term performance
    - especially for implantable devices
  - further evaluate device/component performance
  - evaluate learning curve or training issues
- **FDA and Applicant agree on PAS protocol/outline prior to HDE approval**

# Summary of Safety and Probable Benefit (SSPB)

- FDA's summary of the HDE Submission
- Basis for FDA's approval of HDE
- Contains:
  - device description
  - pre-clinical information
  - clinical information

# Limitations of HDE Approval

- **IRB approval** is required before the HDE-approved device is used
  - approval required at **site**, not for each **patient**
  - except in emergency situations
- Check your IRB Policies

# Limitations of HDE Approval

- **Labeling**
  - must clearly identify device as an HUD
  - must state effectiveness for that indication has not been demonstrated
  - must identify pediatric population, if applicable
- **Profit Restrictions**
  - HDE may not be sold for profit except in certain circumstances.



# HDE Approvals

[www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/HDEApprovals/ucm161827.htm](http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/HDEApprovals/ucm161827.htm)

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Medical Devices

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HDE Approvals

Listing of CDRH Humanitarian Device Exemptions

Listing of CDRH Humanitarian Device Exemptions

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Click the small arrow at the top of each column to sort.

HDE Number	Approval Date and Docket Number	Device Name	Company Name and Address	Device Description / Device Indications
H130006	12/18/15	FENIX™ Continence Restoration System	Torax Medical, Inc. Shoreview, MN 55126	Approval for the FENIX™ Continence Restoration System. This device is indicated for the treatment of fecal incontinence in patients who are not candidates for or have previously failed conservative treatment and less invasive therapy options (e.g. bulking agents, radiofrequency ablation, sacral nerve stimulation).

# HDE Database

## Humanitarian Device Exemption (HDE)

[FDA Home](#)
[Medical Devices](#)
[Databases](#)

**Search Database**
 Help

Applicant	<input type="text"/>	HDE Number	<input type="text"/>
Device	<input type="text"/>	Docket Number	<input type="text"/>
Decision Date	<input type="text"/> to <input type="text"/>	Product Code	<input type="text"/>
Advisory Committee	<input style="border-bottom: 1px solid #ccc; width: 100%;" type="text"/>	Cleared/Approved IVD Products	<input type="checkbox"/>
Supplement Type	<input style="border-bottom: 1px solid #ccc; width: 100%;" type="text"/>	Combination Products	<input type="checkbox"/>
Sort by	<input style="border-bottom: 1px solid #ccc; width: 100%;" type="text"/>	Center	<input style="border-bottom: 1px solid #ccc; width: 100%;" type="text"/>

[Clear Form](#)

[www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfHDE/hde.cfm](http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfHDE/hde.cfm)

# Successful Submission Strategies

- Be organized
- Be prepared
- Be responsive



# Be Organized

- **Well-organized**
- **Administratively- and scientifically-complete submission**
- **Contain:**
  - comprehensive table of contents
  - detailed sections
  - all test reports
  - labeled graphs/tables
  - consecutive page numbers (e.g., 1, 2, 3)

# Be Prepared

- Have your team ready to answer questions
- Have copies of the HDE submission and any other submissions/interactions with FDA (e.g., Pre-Subs)
- Be ready for manufacturing and bioresearch monitoring inspections

# Be Responsive

- **Provide complete and accurate contact information**
  - include email, phone number, and fax number
  - list alternate contact
  - foreign applicant should have a U.S. representative
- **Be upfront and responsive**
  - answer FDA's questions when you say you will
  - if you don't understand a question, call/email and ask
- **Be in touch**
  - discuss questions, concerns with lead reviewer
  - have your subject matter experts available for consult with FDA

# Be Responsive

- **Be ready to interact on labeling**
  - have your decision-makers available for quick turnaround
- **Develop post-approval study plan early**
  - work with the FDA team to gain agreement on post-approval study

# Summary

- An approved HDE authorizes the applicant to market an HUD.
- Basis for approval: reasonable assurance of safety and probable benefit.
- An HDE application consists of information describing the device, and valid scientific evidence to support reasonable safety and probable benefit.



# Summary

- The FDA website contains useful information on the HDE program and approved HDEs.
- The HDE Review Process involves several key decision points and interactions between FDA and the applicant to help complete the review.

# Summary

- The HDE approval package contains the approval order outlining the conditions of approval, the labeling, the SSPB, and consumer information
- A well organized, complete application will assist the review process

# Resources

- **Humanitarian Device Exemption (HDE): Questions and Answers - Draft Guidance for HDE Holders, Institutional Review Boards, Clinical Investigators, and Food and Drug Administration Staff**  
[www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm389154.htm](http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm389154.htm)
- **Guidance for HDE Holders, Institutional Review Boards (IRBs), Clinical Investigators, and FDA Staff - Humanitarian Device Exemption (HDE) Regulation: Questions and Answers**  
[www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm110194.htm](http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm110194.htm)
- **Guidance for Industry and Food and Drug Administration Staff – Humanitarian Use Device (HUD) Designations**  
[www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM336515.pdf](http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM336515.pdf)

# Resources

- **Device Advice – Humanitarian Device Exemption**

[www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/HumanitarianDeviceExemption/default.htm](http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/HumanitarianDeviceExemption/default.htm)

- **HDE Approvals**

[www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/HDEApprovals/default.htm](http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/HDEApprovals/default.htm)

- **HDE Checklist for Filing Decisions**

[www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/HumanitarianDeviceExemption/UCM056830.pdf](http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/HumanitarianDeviceExemption/UCM056830.pdf)

# Providing Industry Education

## 1. CDRH Learn – Multi-Media Industry Education

- over 80 modules - videos, audio recordings, power point presentations, software-based “how to” modules
- accessible on your portable devices: [www.fda.gov/Training/CDRHLearn](http://www.fda.gov/Training/CDRHLearn)

## 2. Device Advice – Text-Based Education

- comprehensive regulatory information on premarket and postmarket topics: [www.fda.gov/MedicalDevices/DeviceRegulationandGuidance](http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance)

## 3. Division of Industry and Consumer Education (DICE)

- If you have a question - Email: [DICE@fda.hhs.gov](mailto:DICE@fda.hhs.gov)
- Phone: 1(800) 638-2041 or (301) 796-7100 (Live Agents 9am–12:30 pm; 1-4:30 pm EST)
- **Web Homepage:**  
[www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/ContactUs--DivisionofIndustryandConsumerEducation/default.htm](http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/ContactUs--DivisionofIndustryandConsumerEducation/default.htm)