Humanitarian Device Exemption (HDE): Post-approval Activities

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Learning Objectives

- Understand the regulatory responsibilities for an approved Humanitarian Device Exemption (HDE)
- Describe the post-approval reporting requirements
- Understand the purpose of the annual incidence reassessment

Learning Objectives

- Understand the different types of HDE Supplements
- Understand the role of the Pediatric Advisory Committee and Institutional Review Boards (IRBs) with HDEs

HDE Post-approval Requirements

- **Post-Approval Requirements specific to HDEs**
  - HDE Supplements (21 CFR 814.108)
  - IRB Approval (21 CFR 814.124)
  - HDE Periodic Reports (21 CFR 814.126)

- **General Requirements for all Medical Devices**
  - Medical Device Reporting (21 CFR 803.50 and 803.52)
  - Recalls (21 CFR 806.10)

Responsibilities of HDE Holders and Institutional Review Boards (IRBs)

HDE Holder Responsibilities

- Ensure that the Humanitarian Use Device (HUD) is used only in **facilities with functioning IRBs**

HDE Holder Responsibilities

- **Maintain records:**
  - names and addresses to which the HUD was shipped
  - correspondence with Institutional Review Boards (IRBs)
  - other information requested by FDA or the reviewing IRB

21 CFR 814.126(b)(2)

IRB Responsibilities

- **IRB Requirements**
  - must have policies for approval and continuing review of HUD
  - may require informed consent prior to use
- **IRB Approval of an HUD at an institution**
  - blanket approval for particular HUD **or**
  - case-by-case basis

Emergency Use of an HUD

- Physician may use HUD if unable to obtain IRB approval prior to use:
  - if patient is at risk of serious harm or death
  - must submit report to IRB chair within 5 days
    - notification of use of device
    - identification of patient
    - date of use
    - reason for use

21 CFR 814.124(a)

Emergency Use of an HUD

- FDA recommends that physician
  - obtain informed consent from patient
  - check with the IRB for any applicable policies
  - maintain patient protection measures
  - submit follow-up report to HDE holder

Research of an HUD

- **Use of Device on-label**
  - for the indications approved under the HDE
  - exempt from the Investigational Device Exemption regulation (21 CFR Part 812)
  - comply with the requirements for IRB review/approval (21 CFR Part 56)
  - comply protection of human subjects (21 CFR Part 50)
- **Use of Device off-label**
  - for an indications other than what was approved under the HDE
  - comply with the IDE regulation (21 CFR Part 812)
  - comply with the requirements for IRB approval (21 CFR Part 56)
  - comply protection of human subjects (21 CFR Part 50)

HDE Reports

- **Termination/Withdrawal of IRB Approval**
- **Periodic Reports**
- **Post-Approval Study Reports**
  - if mandated to conduct a post-approval study

Termination/Withdrawal of IRB Approval

- If IRB withdraws approval of HUD:
  - the holder of the HDE must notify the FDA
  - within **5 working days**

21 CFR 814.124 (b)

FDA Withdraw of an Approved HDE

- after HDE is approved
- another device with same indication may become legally marketed
  - premarket approval (PMA), premarket notification (510(k)), *de novo*
- HUD no longer meets requirements of 520(m)(2)(B)
- FDA may withdraw the HDE

HDE Periodic Reports

- **Device Accountability**
  - number of devices shipped or sold since HDE approval in the calendar year
  - account for multiple devices used in same patient (and vice versa)
- **Clinical Experience**
  - known safety information
  - medical device reports (MDR)
  - data from post-approval studies
  - information that may impact labeling
- **Supplemental Device Changes**

HDE Periodic Reports

Updated information on HUD/HDE Status

- **HDE justification**
  - 21 CFR 814.104(b)(2)
- **Probable benefit outweighs risk**
  - 21 CFR 814.104(b)(3)
- **Annual Incidence Reassessment**
  - 21 CFR 814.126

Annual Incidence Reassessment (AIR)

- Updated **patient population estimate (PPE)** to current U.S. population to ensure that the HUD continues to qualify through the HUD/HDE pathway

- If the PPE exceeds **8000** as a result of the AIR, the HDE may become ineligible for HUD/HDE pathway
  - **Options:** withdraw HDE, convert to treatment IDE, or identify population through new HUD or orphan subset

HDE Periodic Reports: Device Cost

If cost of the device exceeds $250, HDE holder must report:

- assessment completed by an independent Certified Professional Accountant (CPA) or a “responsible individual” of the company
- verifying that the amount charged does not exceed the costs of research, development, fabrication, and distribution

Additional Reports

- **Medical Device Reporting (MDR)** (21 CFR 803)
- **Recall Notification** (21 CFR 806.10)
- **Post-approval Study Reports**

HUD Manufacturer Must Report

- HUD-related deaths, serious injuries, or malfunctions
- Within 30 calendar days
- Based on information which they may receive or otherwise become aware of, from any source,
- Which reasonably suggests that the HUD:
  - May have caused or contributed to a death or serious injury; or
  - Malfunctioned and the malfunction of the device would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

HDE Supplements in the Code of Federal Regulations

Addressed under:

- 21 CFR 814.108
  - "Supplemental applications" under Subpart H (HUDs)
- 21 CFR 814.39
  - "PMA Supplements" under Subpart B (PMAs)

Types of HDE Supplements

- 75-Day Supplement
- 30-Day Notice
- Special HDE Supplement: Changes Being Effected

75-Day Supplements

- Device modifications/Design changes
- Labeling changes
- Manufacturing/Sterilization Site changes
- Post-Approval Study (PAS) Protocol changes
- Requests for annual distribution number (ADN) and profit eligibility
  - modification to ADN

Examples

- Change in materials
- Hardware/software modification
- Extended shelf life

30-Day Notice

- Modifications to manufacturing process

Examples
- Convert a process from manul to automated
- Obtain new manufacturing equipment
- Use an alternate supplier

- FDA may convert to 75-Day PMA Supplement
  - if submission does not qualify for 30-Day Notice

Special HDE Supplement: Changes Being Effected

- Changes that enhance the safety of device

- **Labeling**
  - newly acquired safety-related information not previously submitted to the FDA, and
  - add/strengthen a contraindication, warning, precaution, or information about an adverse reaction.
- **Manufacturing Process Change**
  - generally those that add a step to the quality control or manufacturing processes to enhance safety, but does **not** impact effectiveness

Special HDE Supplement: Changes Being Effected

- Can be implemented prior to FDA approval
- 30-Day review

Examples
- Improved instructions for use
- New quality assurance step

Guidance: 30-Day Notices, 135-Day Premarket Approval (PMA) Supplements and 75-Day Humanitarian Device Exemption (HDE) Supplements for Manufacturing Method or Process Changes

www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080192.htm

HDE Supplements

- **Requests for new/expanded indications for use (IFU) outside of existing HUD designation**
  - **cannot** be submitted as an HDE supplement
  - require a new HUD designation

Pediatric Advisory Committee (PAC)

- Conducts periodic annual review of approved HUDs labeled for pediatric patients that are allowed to make profit
- Ensures that HDE remains appropriate (Section 520(m)(2)) for the pediatric population for which is it approved
  - Section 520(m)(8) of Food, Drug and Cosmetic Act
- FDA's Office of Pediatric Therapeutics (OPT), Office of the Commissioner (OC) coordinates review

PAC Review

- **Information presented to PAC includes:**
  - MDRs received since approval and relevant safety information
  - summary of any post-approval studies
  - summary of relevant peer-reviewed literature published since approval
- **Review Questions**
  - does probable benefit/risk profile of the device for the pediatric population continue to support the HDE for which the exemption was granted

More Information about the PAC:

www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/default.htm

Summary

- A sponsor has a number of regulatory responsibilities after an HDE is approved and for updating FDA on changes to the device
- After approval of an HDE, there are post-approval reporting requirements
- Annual incidence reassessment is an annual estimate of the target population with the disease or condition

Summary

- Modifications that affect the safety and probable benefit of the device require the FDA's review and approval of an HDE Supplement

- Organizations such as the Pediatric Advisory Committee and Institutional Review Boards have specific roles for HDE-approved devices

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

- **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

Resources

- **Device Advice – Humanitarian Device Exemption**

  www.fda.gov/medicaldevices/deviceregulationandguidance/howtomarketyourdevice/premarketsubmissions/humanitariandeviceexemption/default.htm

- **HDE Approvals**

  www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/HDEApprovals/default.htm

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- comprehensive regulatory information on premarket and postmarket topics: **www.fda.gov/MedicalDevices/DeviceRegulationandGuidance**

3. Division of Industry and Consumer Education (DICE)

- If you have a question - Email: **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**