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

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

Examples

- Convert a process from manual to automated
- Obtain new manufacturing equipment
- Use an alternate supplier
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 it is 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
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)