Welcome to today's

FDA/CDRH Webinar

Thank you for your patience while we register all of today's participants.

If you have not connected to the audio portion of the webinar, please do so now:

Dial: 800-369-2039
Passcode: 5179628

Conference Number: PWXW6340800

U.S. FOOD & DRUG ADMINISTRATION

REGULATORY OVERVIEW FOR DEVELOPERS AND SPONSORS OF NEUROLOGICAL DEVICES:

An Introduction to Humanitarian Device Exemptions (HDEs)

Monday, December 18, 2017
12:00PM-1:30PM

Agenda

- Introduction to Humanitarian Device Exemptions
- Humanitarian Use Devices: Program Overview
- Humanitarian Device Exemption and Humanitarian Use Devices: Basics and Pediatric Considerations
- Similarities and Differences between PMAs and HDEs
- HDE Manufacturing Concerns
- HDE Risk Benefit Analysis
- Question & Answer Session

Introduction

Carlos Peña, PhD, MS
Director
Division of Neurological and Physical Medicine Devices
Office of Device Evaluation
Center for Devices and Radiological Health

Introduction

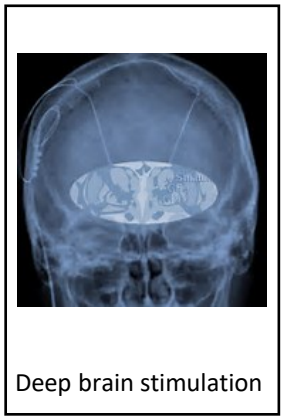
- Patients in the U.S. have access to high-quality, safe, and effective medical devices of public health importance first in the world.
- The U.S. is the world's leader in regulatory science, medical device innovation and manufacturing, and radiation-emitting product safety.
- U.S. post-market surveillance quickly identifies poorly performing devices, accurately characterizes real-world performance, and facilitates device approval or clearance.
- Devices are legally marketed in the U.S. and remain safe, effective, and of high-quality.
- Consumers, patients, their caregivers, and providers have access to understandable science-based information about medical devices and use this information to make health care decisions.

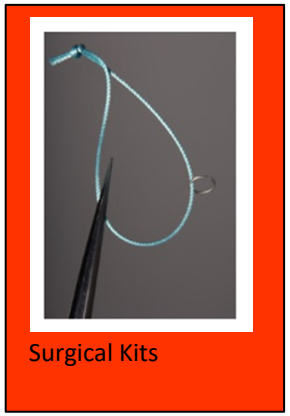
What Is a Medical Device?

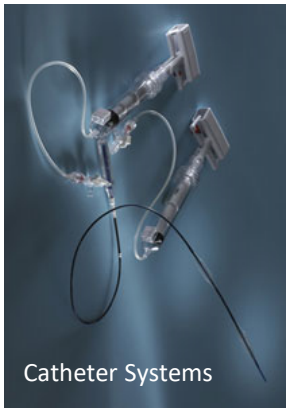
- Definition of a medical device is specified in section 201(h) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 321) *
- Section 201(h) states in part:
  - The term “device”…means an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is…”
  - “…intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man…” or
  - “…intended to affect the structure or any function of the body of man and which does not achieve any of its primary intended purposes through chemical action.…”

Experience in Moving Neurological Medical Devices From **Bench to Market**


Cognitive Function following concussion


Deep brain stimulation


Surgical Kits


Catheter Systems

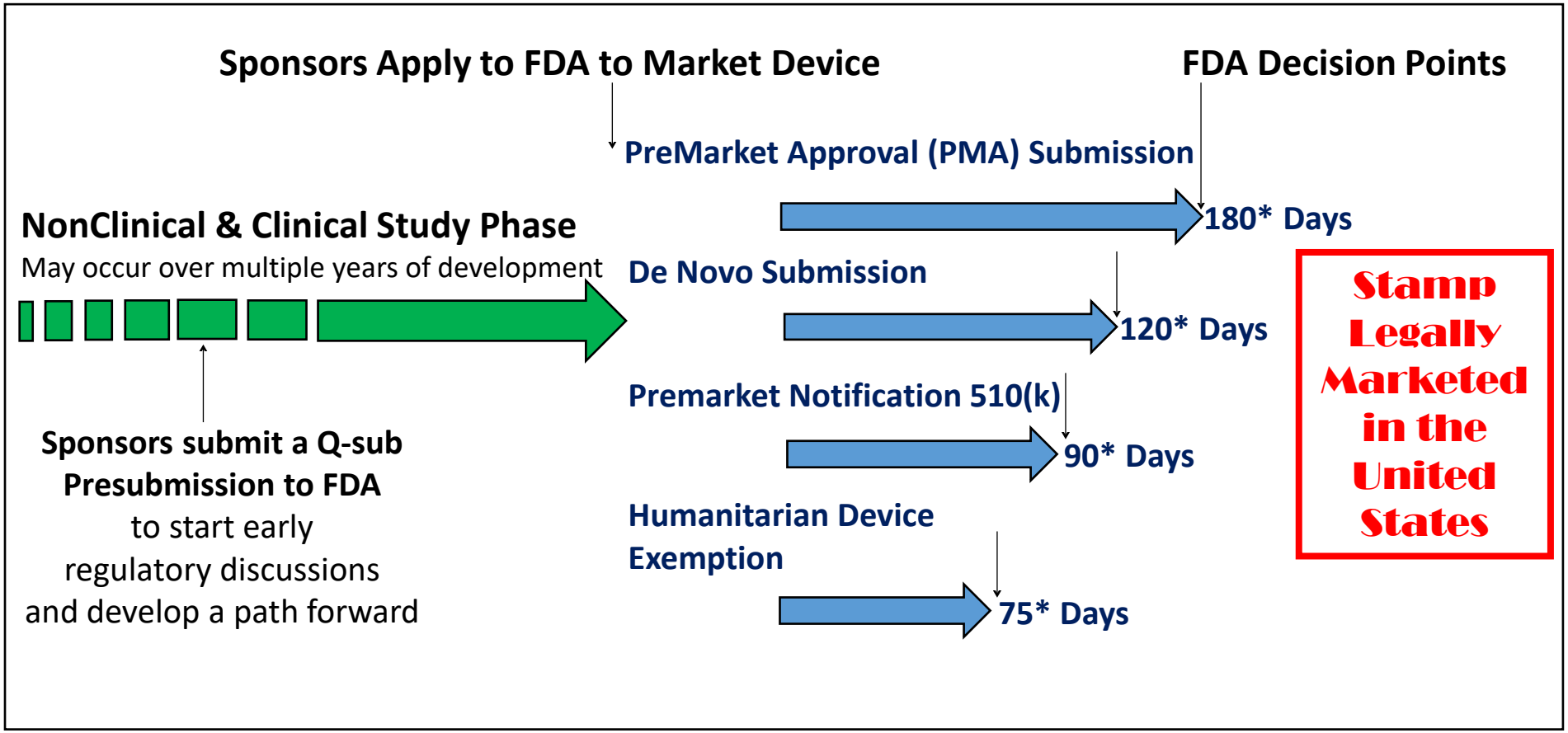

Stent Assisted Coils For Aneurysms


Microcatheters for the neurovasculature

Medical Device Classifications and Regulatory Pathways

- Class III: generally PMA (Premarket Approval)
- Class II: 510(k) (or premarket notification), if the intended use and technology are similar to something already classified
- De Novo: devices that aren't comparable enough to something on the market. This generates a new device classification regulation, and will typically (but not always) be Class II
- Humanitarian Device Exemption (HDE): Regulatory pathway for products intended for diseases or conditions that affect small (rare) populations

Regulatory Pathways for Medical Devices



*Number of days noted is days the submission is under review by the FDA, not the total time that it may take to get the device technology to market or through the review process. In some cases, the review process may take longer depending upon the particular device, technology, indication for use, user, and risk of the device.

Anderson et al., Neuron, 92: 943-948, 2017.

Division of Neurological and Physical Medicine Devices

Neurodiagnostic and Neurosurgical Devices	Neurointerventional Devices	Neurostimulation Devices Neurology Branch	Neurostimulation Devices Psychiatry Branch	Physical Medicine & Rehabilitation Devices
•Cranial Materials & Other Sealants •EEG & Non-EEG Diagnostic Devices •Neurocognitive Diagnostic Devices •Surgical Instruments & Tools for the Neurovasculature •Stereotactic Systems for the Neurovasculature	•Embolization Coils •Flow Diverters •Guidewires & Catheters for the Neurovasculature •Neurothrombectomy Devices •Neurovascular & Cerebral Interventional Devices •Cerebrospinal Fluid Shunts	•Stimulation Devices for Movement Disorders, Epilepsy, Alzheimer's Disease, Headache, and Traumatic Brain Injury •Devices may include cortical stimulation devices and deep brain stimulation devices	•Stimulation Devices for Major Depression, Obsessive Compulsive Disorder, and Post Traumatic Stress Disorder •Devices may include cranial electrical stimulation devices, electroconvulsive therapy, and transcranial magnetic stimulation devices	•Brain Computer Interfaces •Diathermy •Functional Electrical Stimulators •Iontophoresis Devices •Massagers/Vibrators •Orthoses, Exoskeletons •Powered Muscle Stimulators •Rehabilitation Equipment •Wheelchairs, Walkers

Humanitarian Use Devices (HUD): Program Overview

Katie Chowdhury, BSE, MS
Health Science Administrator, Biomedical Engineer
Office of Orphan Products Development
Office of Special Medical Programs

Humanitarian Use Device (HUD) Definition

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

21 CFR 814.3(n)

What are Humanitarian Use Devices?

- In 1990, Congress established the Humanitarian Use Device (HUD) Designation and Humanitarian Device Exemption (HDE) Marketing Pathway
  - designed to encourage the development of devices intended for rare diseases
- General Requirement for a PMA device to enter the market:
  - reasonable assurance that the device is **safe** and **effective**
- Under the HUD/HDE pathway:
  - device is **safe** and provides a **probable benefit**

Getting a HUD to Market

- **Part 1:** Submit a HUD designation request and receive approval from the FDA's Office of Orphan Products Development for the request, and

- **Part 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)

Additional information about the HUD process is available at: https://go.usa.gov/xnksm

HUD Designation by OOPD

- Submit a HUD Designation Request to FDA's Office of Orphan Products Development (OOPD)—two signed and dated submissions (original and eCopy)
- Contents of Request:
  - **A cover letter requesting OOPD consider the device for HUD designation for a rare disease or condition or orphan subset of a disease or condition**
  - **Applicant Contact information**
  - **A description of the disease or condition that the device treats or diagnoses**
  - **The device description as well as a scientific rationale supporting use of the device**
  - **Supporting documentation to demonstrate the device is designed to treat/diagnose a rare disease or condition (or orphan subset) that affects or is manifested not more than 8,000 individuals per year in the United States**

- "Guidance for Industry and FDA Staff: HUD designations" **http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM336515.pdf**

How OOPD Reviews a HUD

- Evaluate disease or condition based upon device functionality
- Estimate target population that may benefit from device
  - Annual Incidence: number of new patients diagnosed with a disease or condition during a particular time period
- May broaden (or reduce) scope of patient population as appropriate
- 45 day review→ Decision letter sent to the applicant

HUD Decisions

- **Options:**
  - Approve
  - Disapprove
  - Request Additional Information

- **Approval: Designate the device for the disease or condition**
  - Population estimate must be not more than 8,000/year in the U.S.
  - If population estimate more than 8,000/year, must show device is an “orphan subset” – use of the device is limited to only a subset of the non-rare disease population
  - Applicant can submit an Humanitarian Device Exemption (HDE) application to CDRH or CBER

Pediatric Considerations

- Younger than 22 years of age
- Device may be eligible if the pediatric population affected by the disease or condition is not more than 8,000 individuals per year
- OOPD will designate a device solely for pediatric use if it qualifies based upon the population estimate

Humanitarian Device Exemption and Humanitarian Use Devices: Basics and Pediatric Considerations

Anupama Govindarajan, PhD
Neurostimulation Devices Psychiatry Branch
Office of Device Evaluation
Center for Devices and Radiological Health

Humanitarian Use Device (HUD) Designations and Humanitarian Device Exemptions (HDEs)

Rationale: Rare diseases or conditions can be a devastating occurrence for the patient and their family.

HUD: 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.

HDE: An HDE is a marketing application for an HUD. An HDE is exempt from the effectiveness requirements of Sections 514 and 515 of the FD&C Act, and it's subject to certain profit and use restrictions.

Getting an HDE to Market

Step 1: Obtain an HUD designation from the FDA's Office of Orphan Products (OOPD)

Step 2: Submit an HDE

- **HDE Eligibility:**
  - A device is eligible for review in an HDE application if it meets two criteria:
  - Device receives HUD designation.
  - There is no comparable legally marketed device for the same disease or condition granted under another regulatory pathway.

HDE Approval Threshold

Approval is based on two factors:

- A reasonable assurance of safety. Reasonable assurance of safety consists of not posing an unreasonable risk of illness or injury to the patient.
- A demonstration of probable benefit.

The basis to approve an HDE is the demonstration that the use of the device, or its probable benefit, outweighs the risk of injury or illness from its use. This also takes into account considerations whether other available options are available as well as their respective benefits and risks.

What if Other Devices are Already Marketed for a Similar Indication?

FDA will only consider HDE applications if there "is no comparable device available to treat or diagnose the disease or condition," unless the comparable device is also approved under an HDE or is still in a testing phase under an investigational device exemption (IDE).

"Comparable device" does not necessarily mean "identical"

What Should Be Included in an HDE Application?

- A copy or reference to the approved HUD designation letter
- Explanation of why the device is not otherwise available and a statement that no comparable device is legally marketed.
- Device description, including a discussion of all device components and accessories and how they work.
- Proposed indications for use
- Valid scientific evidence to support the safety and probable benefit of the device.
- Manufacturing information

What Should Be Included in an HDE Application? Cont.

- The amount to be charged for the device, as well as (if it's more than $250) a statement indicating that the cost of the device does not "exceed the costs of the device's research, development, fabrication and distribution."

- The application should include physician labeling and, if applicable, patient labeling.

- Labeling that the device is a humanitarian use device and that, although the device is authorized by federal law, the effectiveness of the device for the specific indication has not been demonstrated.

- Clinical evidence submitted in the HDE should preferably include summaries, conclusions, and results of all clinical experience or investigations.

HDE Application – Clinical Study Limitations

- The FDA recognizes that there may be limitations and challenges in the collection of relevant clinical evidence for an HDE device.

- Challenges may arise in the recruitment of patients into a clinical study, in some cases leading to smaller sample sizes in a prospective clinical study.

Pediatric Requirements for HDEs

March 2014 - Premarket Assessment of Pediatric Medical Devices: Guidance for Industry and FDA Staff - https://go.usa.gov/xnkep

FDA defines pediatric populations as:

- neonates (0-28 days)
- infants (<2 years)
- children (2-12 years of age)
- adolescents under 21 years of age

Section 515A of the Food and Drug Administration Safety and Innovation Act (FDASIA) requests the following information:

- description of any pediatric subpopulations that suffer from the disease or condition that the device is intended to treat, diagnose, or cure
- number of affected pediatric patients
- device labeling must clearly identify the device as an HUD. It must state that the effectiveness for that indication has not been demonstrated. The labeling must identify the pediatric population if the HDE was approved for a specific pediatric indication.

Similarities and Differences Between Premarket Approvals (PMAs) and HDEs

LT Kelliann Wachrathit
Biomedical Engineer
Physical Medicine and Rehabilitation Devices Branch
Division of Neurological and Physical Medicine Devices
Office of Device Evaluation
Center for Devices and Radiological Health

Comparing PMAs and HDEs

	PMA	HDE
Indications for Use	Proposed by applicant	Based on HUD designation
Safety	Reasonable assurance of safety	Will not expose patients to an unreasonable or significant risk of illness or injury
Effectiveness	Reasonable assurance of effectiveness	Demonstration of **probable benefit**. Exempt from demonstrating effectiveness.
FDA review days	180 days – if no panel 320 days – if panel	Typically 75 FDA days to determine a decision
Institutional Review Board (IRB) oversight after approval	No	Yes, may **only** be used at facilities that have IRB oversight
Restrictions on profit	No	Yes

Similarities Between PMAs and HDEs

- Filing review completed in the first 30 days
- May be submitted as a modular submission (https://go.usa.gov/xnkeF)
- Quality Systems Regulation (QSR) (21CFR Part 820) apply to both PMAs and HDEs
- Publically available documents posted after approval
  - Summaries
    - "Summary of Safety and Effectiveness Data (SSED)" posted after PMA approval
    - "Summary of Safety and Probable Benefit (SSPB)" posted after HDE approval
  - Approval Orders
  - Labeling
  - Consumer Information
- Post-market activities
  - Conditions of Approval (e.g. Post Approval studies)
  - Annual Reports
  - Requires supplements for changes

Differences Between PMAs and HDEs

- First Step for HDE - Obtain a HUD Designation
- No user fees for HDEs
- HDEs are exempt from demonstrating effectiveness and should demonstrate **probable** benefit
- Approved HDE devices are unclassified
- Post-market limitations
  - IRB approval is required before the HDE-approved device is used at a clinical site
  - Labeling
  - Profit Restrictions

Differences Between PMAs and HDEs, Cont.

- HDEs cannot be approved once a comparable device with the same indications for use is marketed through a PMA or 510(K)

- Compassionate Use provisions may be applied to HDE devices
  - Patients may have access to investigational devices that have not received FDA approval or clearance for patients for whom the treating physician believes the device may provide a benefit in treating and/or diagnosing their disease or condition.

Transitions Between PMAs and HDEs

- A PMA may be submitted for an HDE device when seeking a different indication for use that manifests in **more than** 8000 individuals per year

- Data can be collected in a clinical investigation for the **HDE-approved indication(s)** without an IDE
  - The safety and effectiveness data may be used to support a future PMA for the HDE-approved indication(s)

U.S. FOOD & DRUG ADMINISTRATION

Humanitarian Device Exemption (HDE) Manufacturing Information

Matthew Krueger
Chief
Physical Medicine, Orthopedic, Neurology, and Dental Devices Branch
Division of Manufacturing and Quality
Office of Compliance
Center for Devices and Radiological Health (CDRH)

Manufacturing Related Submissions

- Original/Modular HDEs
- Pre-approval Inspections
- Site Change Supplements
- 30-Day Notices

Comparison to PMA Submissions

Similarities	Differences
• Manufacturing information required in submission is the same as for a PMA • Manufacturing changes that require a submission are the same as for a PMA	• Review timeframe for an HDE is generally shorter than for a PMA

PMA vs. HDE Manufacturing Review Comparison

Submission	HDE	PMA
Original	75 Days	180 Days
Modular	90 Days	90 Days
Site Change Supplement	75 Days	180 Days
30-Day Notice (Mfg Change)	30 Days	30 Days

Manufacturing Information to Submit in an HDE

- Same manufacturing information provided in PMAs and PMA supplements

- Guidance Documents:
  - "Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff" dated February 3, 2003
    - https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070899.pdf
  - 30-Day Notices, 135-Day Premarket Approval (PMA) Supplements and 75-Day Humanitarian Device Exemption (HDE) Supplements for Manufacturing Method or Process Changes
    - https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM080194.pdf

U.S. FOOD & DRUG ADMINISTRATION

Humanitarian Device Exemption (HDE) Risk Benefit Analysis

Gregg Kittlesen

Materials Engineer

Neurodiagnostic and Neurosurgical Devices Branch

Division of Neurological and Physical Medicine Devices

Office of Device Evaluation

Center for Devices and Radiological Health

Examples of Neurological Device HDEs

Neurointerventional Devices

- Stents
- Embolics
- Balloons for specified endovascular treatments

Neurosurgical Devices

- Surgical devices for creating specified arteriotomies

Neuromodulation Devices

- Deep brain stimulation
- Intramuscular stimulation devices
- Other stimulation device types

Examples of Clinical Trial Designs for Neurological Devices

- Prospective, multi-center, clinical studies
- Single-arm, non-randomized trial designs
- Study size patient numbers can range depending upon the proposed indications for use
- Follow-up ranges dependent on safety questions

Example Safety Data for Neurological Device HDEs

Most Common Adverse Events	Observation
Headache	---
Respiratory problems	---
Stroke	---
Nausea	---
Hypotension	---
Shortness of breath	---

Severe Adverse Events	Observations
Neurologic death	---
Major debilitating stroke	---
Stroke	---

Example Probable Benefit Data for Neurological Device HDEs

Attribute	Observation
Aneurysm occlusion rate (Raymond I or II) at 180 days post-procedure (100% or near complete occlusion)	---
Observed adverse events and associated rates of adverse events	---
Favorable clinical outcome (mRS 0-2) at 180 days post-procedure (measure of functional independence and disability)	---

FDA U.S. FOOD & DRUG ADMINISTRATION

Post Market Activities For Humanitarian Use Devices and Humanitarian Device Exemptions

Michael Hoffmann
Deputy Director for Regulatory Policy
Division of Neurological and Physical Medicine Devices
Office of Device Evaluation
Center for Devices and Radiological Health

Institutional Review Board (IRB) Review

- After HDE approval, the device may only be used after IRB approval has been obtained for the use of the device at a clinical site, for the FDA-approved indication, except for an emergency use situation.

- A HUD used in a clinical investigation is considered to be used for "investigational use", whether or not the device is used for the HDE-approved indication. Such investigational use is subject to the same requirements that apply to all FDA-regulated clinical studies, including
  - 21 CFR Part 50 (Protection of Human Subjects) and
  - 21 CFR Part 56 (Institutional Review Boards).

- If the HUD is being studied for a use *other than* its approved indication, the IDE regulations also apply.

IRB Review, Cont.

- The HDE holder is responsible for ensuring that a HUD approved under an HDE is administered only in facilities having IRB oversight and acting in accordance with the Agency's regulation governing IRBs

- IRBs are responsible for initial and continuing review of the HUD. Initial review of an HUD must be performed at an IRB's convened meeting.
  - IRB may give blanket approval for the use of a particular HDE device at an institution, or it may give approval on a case-by-case basis.

Pediatric Advisory Committee

- 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.
- FDA's Office of Pediatric Therapeutics (OPT), Office of the Commissioner 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

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

Annual Reports

According to CFR 814.126, annual reports must include:

1. Updated annual incidence reassessment (AIR)

2. Updated explanation of:
   - why the device would not be available unless an HDE were granted, **and**
   - 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

Annual Reports, Cont.

3. Updated explanation why probable benefits to health 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
4. Updated amount to be charged for the device
   - If > $250, a report by an independent certified public accountant or an attestation by a responsible individual of the organization
5. Number of devices that have been shipped or sold since initial marketing approval
   - If > 8,000, an explanation and estimate of number of devices used per patient

Annual Reports, Cont.

6. 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

7. A summary of any changes made to the device in accordance with supplements submitted under 21 CFR 814.108

After the HDE Approval

- Assessing Use of the Device Annually
- Premarket Application Options
- Engaging FDA via Presubmissions

Questions?

Division of Industry and Consumer Education: DICE@fda.hhs.gov

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

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

Under the Heading: How to Study and Market Your Device

Please complete a short survey about your FDA CDRH webinar experience. The survey can be found at www.fda.gov/CDRHWebinar

immediately following the conclusion of the live webinar.