Premarket Approval & Humanitarian Device Exemption Applications

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Disclaimer

The views expressed here are solely mine and not of my firm or any of its clients.

Outline

1. Definitions
2. Premarket Approval Application (PMA)
3. Humanitarian Device Exemption Application (HDE)
4. Breakthrough and Safer Designations for Submissions
5. Key Takeaways
6. Key FDA Resources

Definitions

- CFR ≡ Code of Federal Regulations (21 CFR)
- CRF ≡ Case Report Form
- FDCA ≡ Federal Food Drug & Cosmetic Act
- FY ≡ Fiscal Year is from Oct. 1st to Sept. 30th
- IDE ≡ Investigational Device Exemption application
- IRB ≡ Institutional Review Board
- OCE ≡ Office of Communication and Education
- OPEQ ≡ Office of Product Evaluation and Quality
- OSEL ≡ Office of Science and Engineering Laboratories
- QSR ≡ Quality System Regulation
- Q-Sub ≡ Pre-submission feedback program

Premarket Approval Application (PMA)

PMA

Number of Original PMAs and Panel-track Supplements*		
Review Office	**FY 2020**	**FY 2021**
OHT1	6	8
OHT2	23	19
OHT3	7	4
OHT4	5	6
OHT5	4	9
OHT6	2	4
OHT7	30	28
Total PMAs	77	78
510(k)s	3700	3985
De Novos	69	63

***Number Received by CDRH,** per Feb. 2022 Performance Report

Original PMA (when applicable)

Class III device (FDCA 513(a)(1)(C) and CFR 860.3 (c)(3)):

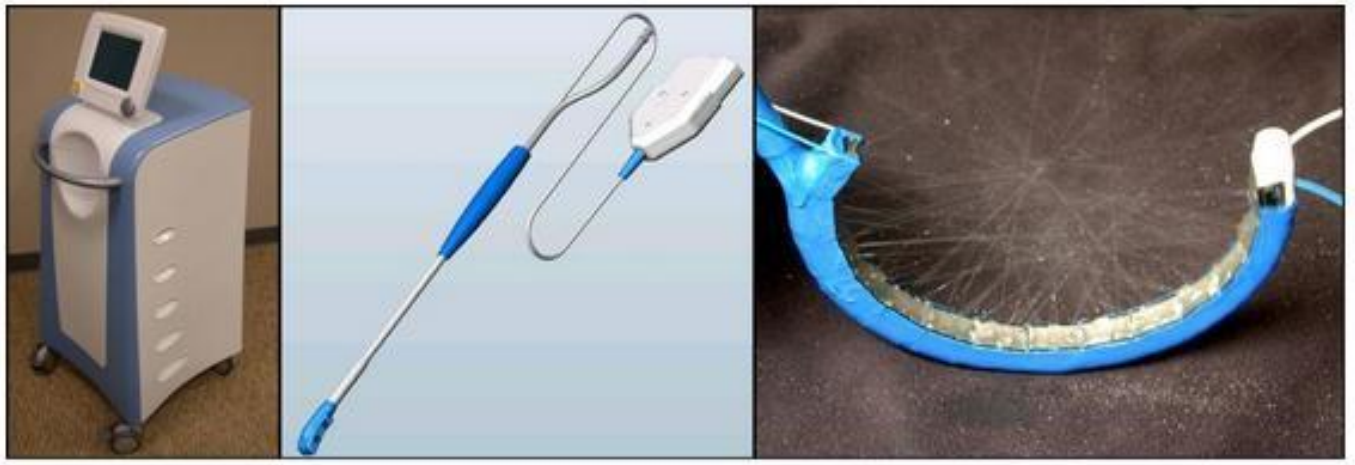
1. General Controls are insufficient (Not Class I);
2. General and Special Controls are insufficient (Not Class II); and,
3. One of the following:
    a. life-supporting,
    b. life-sustaining,
    c. of substantial importance in preventing impairment of human health, or
    d. if presents a potential unreasonable risk.

Classification Polling Question - Background

The Epicor™ Ablation System is intended for ablating cardiac tissue.

- *Physical State*: Tip (c) delivers focused energy to ablate the tissue. Tip goes around the beating heart.
- *Technical Method:* Device delivers high frequency focused ultrasound (HIFU) to heat and create lesion at the target tissue volume.

Epicor™ System Console (a), Epicor™ UltraWand LP (b) and medical UltraCinch LP ablation device (c).
LP: low profile.



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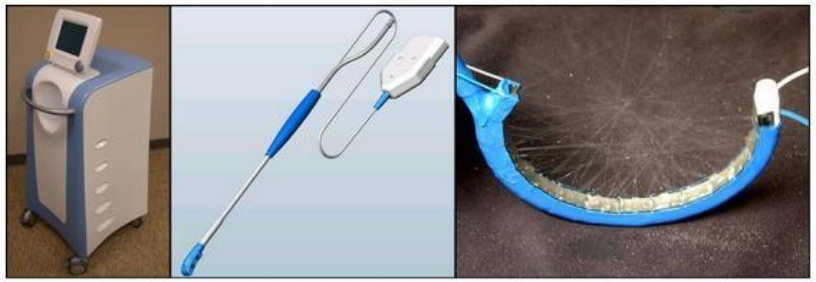
Epicor™ Ablation System



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What is the Class that FDA would likely assign to device?

Please choose one of the following:

1. Class I (general controls are sufficient);
2. Class II (general and special controls are sufficient);
3. Class III (general and PMA controls); or,
4. I need to confirm some details first [please type your question in Q/A].

Original PMA (contents)

Contents (FDCA 515(c) and CFR 814.20)

1. Summary of safety and effectiveness data (SSED);
2. Indications;
3. Device Description (reference Master File(s));
4. Preclinical data;
5. Clinical data (valid scientific evidence);
6. Labeling;
7. Manufacturing;
8. Post-approval study proposal;
9. …

Original PMA (contents)

Clinical data-valid scientific evidence (FDCA 513(a)(3) and CFR 860.7(c)(2)):

- well-controlled investigations;
- partially controlled studies (in CFR);
- studies and objective trials without matched controls (in CFR);
- well-documented case histories conducted by qualified experts (in CFR); and/or
- reports of significant human experience with a marketed device (in CFR).

And, data may be from Outside U.S. (CFR 814.15).

Original PMA (submission options)

- Modular
  1. shell,
  2. device description,
  3. bench testing,
  4. manufacturing info,
  5. …, and
  6. clinical and labeling.
- Traditional

Contents of an Original PMA

1. Indications;
2. Device Description;
3. Preclinical data
   - Biocompatibility;
   - Sterilization and packaging;
   - Bench performance;
   - Software information;
   - Cybersecurity documentation;
   - ….
4. Clinical data (valid scientific evidence);
5. Labeling [+ OCE];
6. Manufacturing;
7. Postmarket study proposal;
8. …

Original PMA (FDA review team)

Engineer (BioMed)

Lead reviewer/ Project manager

Statistician

Engineer (Mechanical)

Scientist (Toxicologist)

Consumer safety officer

OSEL Scientist

Epidemiologist

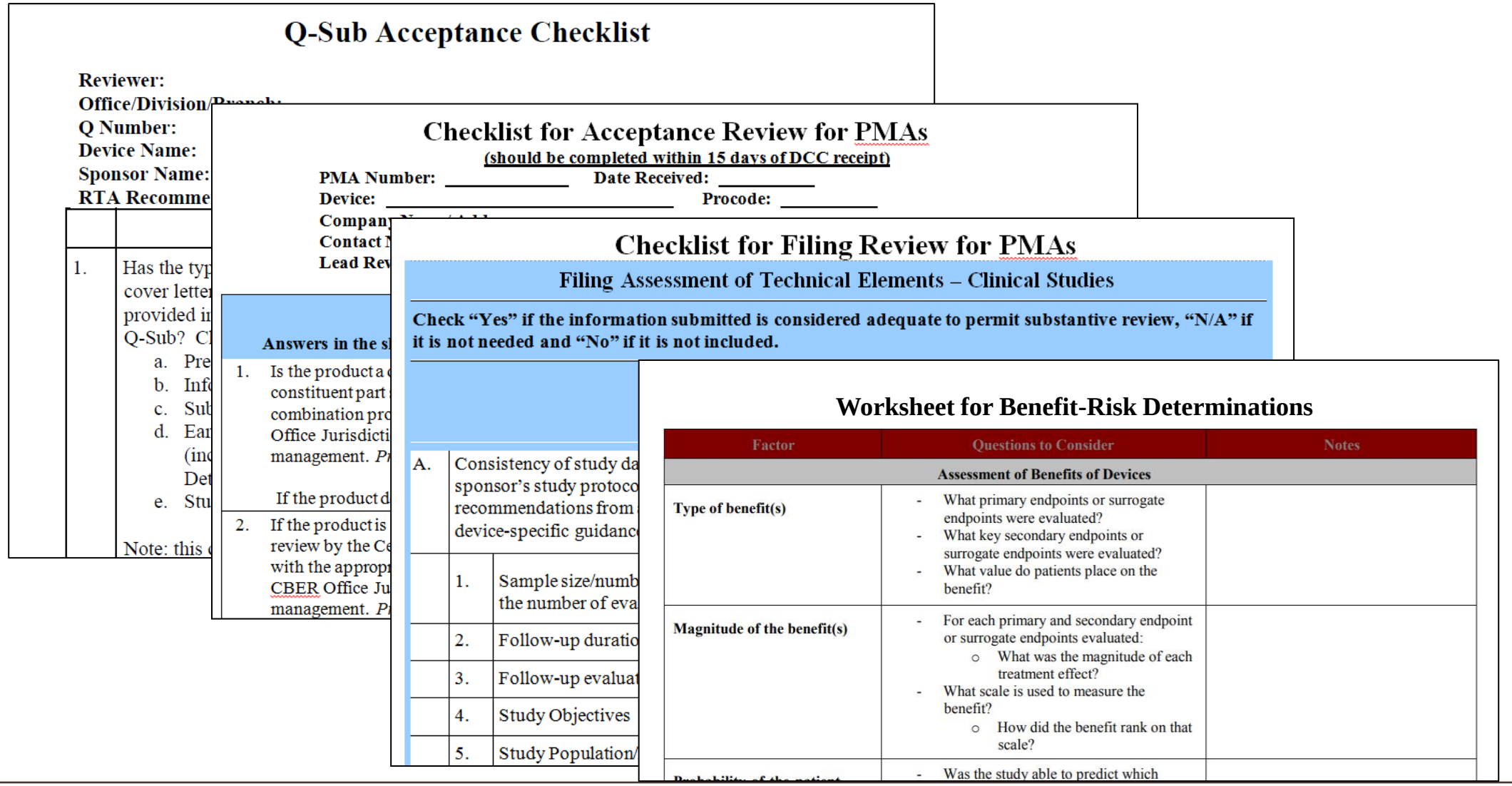
Medical officer

OCE Communication specialist

Scientist (Microbiologist)

Original PMA (FDA advisory panel)

Original PMA (FDA review process)



Q-Sub Acceptance Checklist

Reviewer:
Office/Division/Branch:
Q Number:
Device Name:
Sponsor Name:
RTA Recomme

1.	Has the typ cover letter provided in Q-Sub? Cl a. Pre b. Info c. Sub d. Ear (inc Det e. Stu Note: this

Checklist for Acceptance Review for PMAs

(should be completed within 15 days of DCC receipt)

PMA Number: _____ Date Received: _____
Device: _____ Procode: _____
Company
Contact
Lead Rev

Answers in the s	
1.	Is the product a constituent part combination pro Office Jurisdicti management. *Pr* If the product d
2.	If the product is review by the Ce with the appropr CBER Office Ju management. *Pr*

Checklist for Filing Review for PMAs

Filing Assessment of Technical Elements – Clinical Studies

Check "Yes" if the information submitted is considered adequate to permit substantive review, "N/A" if it is not needed and "No" if it is not included.

A.	Consistency of study da sponsor's study protoco recommendations from device-specific guidanc	
	1.	Sample size/numb the number of eva
	2.	Follow-up duratio
	3.	Follow-up evaluat
	4.	Study Objectives
	5.	Study Population/

Worksheet for Benefit-Risk Determinations

Factor	Questions to Consider	Notes
Assessment of Benefits of Devices		
Type of benefit(s)	- What primary endpoints or surrogate endpoints were evaluated? - What key secondary endpoints or surrogate endpoints were evaluated? - What value do patients place on the benefit?	
Magnitude of the benefit(s)	- For each primary and secondary endpoint or surrogate endpoints evaluated: o What was the magnitude of each treatment effect? - What scale is used to measure the benefit? o How did the benefit rank on that scale?	
Probability of the patient	- Was the study able to predict which	

Original PMA (FDA review timeline)

1. Pre-PMA Q-Sub (within 75 days)
2. Acceptance Review (within 15 days – FDA review clock starts here at receipt date if PMA is accepted and filed.)
3. Filing Review (within 45 days of receipt)
4. Substantive Review (within 90 days of receipt)
    a. Major deficiency letter
        i. Stops FDA review clock;
        ii. Requires a Major Amendment with complete response to restart review clock.
    b. Minor deficiency email/call
5. Day 100 Meeting (if applicant requested)
6. Advisory Panel Meeting (as needed)
    a. Major deficiency letter, or
    b. Minor deficiency email/call
7. Decision
    a. No panel meeting (within 180 days)
    b. Panel meeting (within 320 days)

Original PMA (Panel Review)

Advisory Panel Meeting (FDCA Sec. 515(c)(3)(B) & (f)(2)(B) and 21 CFR 814.44 and 814.116)

1. FDA convenes panel meeting when:
    - Device is first of its kind;
    - Concerns with performance, outcomes or study conducts; and/or
    - At the request of PMA applicant.

2. Panel constituents (Special Govn. Employees- SGEs 5 CFR 2640.103(a)(1)):
    - Practitioners;
    - Biostatistician(s);
    - Technical expert(s);
    - Patient/consumer representative*;
    - Industry representative*;
    - FDA Office Director; and
    - FDA Designated Officer (DFO)

*Not SGE

Original PMA (Panel Review, cont'd)

Advisory Panel Meeting (FDCA Sec. 515(c)(3)(B) & (f)(2)(B) and 21 CFR 814.44 and 814.116)

3. Pre-meeting, applicant interacts with DFO on Panel Pack:
    - Provide requested redacted/unredacted materials such as Executive Summary, PMA application, IDE protocol, Labeling, CRFs of certain subjects;
    - Comment on FDA Executive Summary (respond to FDA comments on applicant's Executive Summary); and,
    - Comment on FDA questions for the panel.

4. Panel Meeting process:
    1. Applicant presentation;
    2. FDA presentation;
    3. Open public hearing;
    4. Panel deliberations and answering FDA questions; and.
    5. Panel Voting.

Original PMA (FDA review considerations)

Safety and Effectiveness evaluation (FDCA Sec. 513(a)(2) and 21 CFR 860.7(b))

1. Intended patient population;
2. Intended conditions of use;
3. Weighing probable benefit against probable risk of injury or illness; and,
4. Reliability of the device (in CFR)

Original PMA (FDA review considerations, cont'd)

PMA approval is based on (FDCA 515(d)(1)(A)(i) and 814.44 (d)(1)):

1. Reasonable assurance of device safety;
2. Reasonable assurance of device effectiveness;
3. Good manufacturing practices (FDCA 520(f) and CFR 820);
4. True and accurate labeling (per CFR 801 or 809); and
5. …

Original PMA (FDA review considerations, cont'd)

- Reasonable Assurance of Safety: when "it can be determined, based upon valid scientific evidence, that the probable benefits … outweigh any probable risks." (21 CFR 860.7(d)(1))

- Reasonable Assurance of Effectiveness: when "it can be determined, based upon valid scientific evidence that in a significant portion of the target population… the use of the device for its intended uses … will provide clinically significant results." (21 CFR 860.7(e)(1))

Original PMA (FDA review considerations, cont'd)

Other Approval Considerations for PMA Order:

- Extrapolate to pediatric population (FDCA 515A (b))
- Conditions of approval (CFR 814.82)
  - Restrictions of the sale, distribution or use (FDCA 515(d)(1)(B)(ii) and 520(e))
  - Post-approval study
  - Post-market surveillance (522) study (FDCA 522)
  - Tracking (FDCA 519(e) and CFR 821)
  - …

FDA Decision On PMA

- Approval with conditions (21CFR 814.44 (d))
- Approvable pending… (21CFR 814.44 (e))
  - QSR inspection
  - Agreement to approval conditions
  - …
- Not approvable (21CFR 814.44 (f))
  - major deficiencies
- Denial of approval (21CFR 814.45)

Polling Question on Post-Approval Changes

Post-approval, the PMA device, its manufacturing process, and/or its labeling can be modified, when…

Please choose one of the following:

1. FDA has provided approval for the change;
2. The company determines that the change is to enhance safety or can be evaluated by an already approved method (i.e., no prior FDA-approval is needed);
3. The change is to be eventually reported to FDA within the allotted time period (such as annually by the date of the original approval);
4. None of the above; or,
5. All of the above.

Post-Approval: PMA Submissions for Changes

(FDCA 515(d)(6) and CFR814.39)

- Amendment (update to ownership, contact info.)
- Special supplement (certain labeling and manufacturing changes - 30 day)
- 30-day notice (minor manufacturing change)
- 135-day supplement (manufacturing change not qualified for 30-day notice)
- 180-day site change supplement
- Real time supplement (minor change - 90 day)
- 180-day supplement (significant change(s) that could affect safety or effectiveness)
  - Real World Evidence (significant labeling change(s))
- Panel-Track supplement (new indication – same clock as an Original PMA)

PMA Annual Reports (FDCA 515(d)(6) and CFR814.39)

1. "Regular" annual report contains:
   - Changes FDA has approved or still under review;
   - Changes implemented without FDA approval with justifications;
   - Summary and bibliography of unpublished and published information on device, which were not previously submitted; and
   - Number of devices shipped or sold.

2. Post-approval study report

Humanitarian Device Exemption Application (HDE)

HDE

Number of Original HDEs*		
Review Office	**FY 2020**	**FY 2021**
OHT1		
OHT2		
OHT3		1
OHT4		
OHT5		
OHT6		2
OHT7		
Total HDEs	**0**	**3**

***Number Approved** per CDRH Database; number received is likely higher

Original HDE (when applicable)

Class III Humanitarian Use Device (HUD)

—HUD designation from FDA/Office of Orphan Products Development (OOPD)

—HUD criteria (FDCA 520(m) and CFR 814.102) :

- Incidence rate of < 8000 patients per year; and,
- No other legally marketed, "non-HUD" device for the intended use.

Original HDE (contents - CFR 814.104)

1. OOPD's HUD Designation Letter with Annual Distribution Number (ADN);
2. Explanations for need of HDE;
3. Summary of safety and probable benefit (SSPB)
4. Indications;
5. Device Description;
6. Preclinical data [+ OSEL];
7. Clinical data (valid scientific evidence);
8. Labeling [+ OCE];
9. Manufacturing;
10. Postmarket study proposal;
11. …

Original HDE (FDA review teams)

Same as PMA:

Original HDE (FDA review process)

1. Filing Review (within 30 days - CFR 814.112)
2. Advisory Panel Meeting (if needed)
    a. Major deficiency letter

        Major Amendment will reset FDA review clock back to 75 days.

    b. Minor deficiency email/calls
3. Decision (within 75 days per FDCA 520(m)(2) and CFR 814.114)
    - Actual duration was ~8 mos. for one HDE and ~20 mos. for two HDEs approved in 2021.

Original HDE (FDA review considerations)

HDE approval is based on (FDCA 520(m) and CFR 814.118):

1. Reasonable assurance of device safety;
2. Probable benefit to health;
3. Good manufacturing practices (FDCA 520(f) and CFR 820);
4. True and accurate labeling (per CFR 801 or 809);
5. …

Original HDE (FDA review considerations, cont'd)

Other Approval Considerations for HDE Order (same as PMA):

- Extrapolate to pediatric population (FDCA 515A (b))
- Conditions of approval (CFR 814.116 (c))
  - Restrictions of the sale, distribution or use (FDCA 515(d)(1)(B)(ii) and 520(e))
  - Post-approval study
  - Post-market surveillance study (FDCA 522)
  - Tracking (FDCA 519(e) and CFR 821)
  - …

FDA Decisions On HDE (same as PMA)

- Approval with conditions (21CFR 814.116 (b))
- Approvable pending… (21CFR 814.116 (c))
  - QSR inspection
  - Agreement to approval conditions
  - …
- Not approvable (21CFR 814.116 (d))
  - major deficiencies
- Denial of approval (21CFR 814.118)

HDE Submissions for Post-Approval Changes (CFR814.108)

- 30 day notice (minor manufacturing change)
- 75 day supplement (manufacturing change not qualified for 30 day notice)
- 75 day supplement (design or labeling change)

➢ New indication for an HDE device requires new HUD and HDE.

HDE Annual Reports (CFR814.126(b))

1. "Regular" annual report contains:
   - Updated annual incidence reassessment (AIR) to justify HUD designation;
   - Updated explanations of HDE eligibility;
   - Updated analysis of risks and benefits;
   - Amount charged and justifications if over $250;
   - Number of devices shipped or sold;
   - Clinical experience with device; and
   - Summary of changes implemented following approved supplements.

2. Post-approval study report

HDE (postmarket considerations)

Restrictions on HDE-approved device (FDCA 520(m)):

- No profit on sales,
  - Unless intended for pediatric patients (*subject to annual review by Pediatric Advisory Panel*);
- IRB approval and monitoring (FDCA 520 (m) (4) and CFR814.124); and,
- Not exceeding ADN.

HDE (postmarket considerations, cont'd)

Withdrawal of HDE Approval Order when a comparable device is PMA- approved for the same intended use (FDCA 520(m)(2)(B))

Breakthrough and Safer Designations

Breakthrough Device

(FDA 2018 Guidance)

Breakthrough Device Designation (FDCA 515(c) – to be requested in a Q-Sub)

1. Provide for more effective treatment or diagnosis of life-threatening or irreversibly debilitating disease or conditions; and

2. one of the following:
   a. breakthrough technology;
   b. no approved alternative;
   c. offers significant [clinically meaningful] advantages over existing approved or cleared alternatives; or
   d. availability is in the best interest of patients.

Breakthrough PMA (how it's reviewed?)

PMA Process but Approval could be based on:

1. Intermediate or Surrogate endpoints
2. Smaller sample in premarket phase (with additional data in postmarket phase)
3. Less manufacturing information in PMA (if company has a good QSR track record)
4. No pre-approval inspection of facility (with good inspectional history)

Safer Technologies Program (STeP)

(FDA 2021 Guidance)

STeP Designation (to be requested in a Q-Sub):

1. Not eligible for Breakthrough Designation due to the less serious nature of the disease or condition; and,

2. Safer ("significantly improve benefit-risk") treatment or diagnostic in one of the following areas:
   a. Reducing occurrence of a known serious adverse event;
   b. Reducing occurrence of a known failure mode;
   c. Reducing occurrence of a known use-related hazard or use error; or
   d. Improving the safety of another device or intervention.

STeP PMA (how it's reviewed?)

PMA Process but Approval could be based on:

1. Less manufacturing information in PMA (if company has a good QSR track record)
2. No pre-approval inspection of facility (with good inspectional history)

Polling Question on Breakthrough and STeP

The applicant should submit the Q-Sub to request Breakthrough or STeP Designation…

Please choose one of the following:

1. Once preliminary results are available (during the IDE stage or sooner);
2. As a part of the Pre-PMA Q-Sub; or,
3. At any time while FDA is reviewing the PMA submission.

Key Takeaways

- Each pathway has its own set of requirements.
- Write submission to address each requirement.
- Use language from FDA’s checklist or guidance, if available, to help form the arguments and justifications.

Key Resources

- FDA 'Device Advice' on PMA, https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/default.htm
- FDA 'Device Advice' on HDE, https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/HumanitarianDeviceExemption/default.htm
- Consideration of Uncertainty in Making Benefit-Risk Determinations in Medical Device Premarket Approvals, De Novo Classifications, and Humanitarian Device Exemptions, final guidance issued on August 2019, https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM619220.pdf
- Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision-Making Process, https://www.fda.gov/regulatory-information/search-fda-guidance-documents/modifications-devices-subject-premarket-approval-pma-pma-supplement-decision-making-process
- Breakthrough Devices Program, https://www.fda.gov/regulatory-information/search-fda-guidance-documents/breakthrough-devices-program
- Safer Technologies Program (STeP), https://www.fda.gov/medical-devices/how-study-and-market-your-device/safer-technologies-program-step-medical-devices

Thanks!

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