Morgan Lewis

Navigating the FDA: Moving from Product Concept through Agency Review and Clearance/Approval

Presenters:

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PITTSBURGH Life Sciences GREENHOUSE

- In cooperation

Biographies

M. Elizabeth Bierman
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- M. Elizabeth Bierman is a partner in the FDA/Healthcare Practice. She has more than 20 years of experience in representing domestic and international companies with respect to all FDA regulatory and compliance matters relating to the development, manufacturing, and marketing of medical devices; pharmaceuticals; biologicals; combination products; medical foods; and infant formulas.
- Ms. Bierman has counseled extensively on jurisdictional issues and regulatory pathway strategies for FDA-regulated products; assisted clients in preparing medical device product applications, requests for designation, and other regulatory submissions; conducted FDA regulatory due diligence; and advised on medical device postmarket compliance issues (labeling/promotion, MDRs, recalls, QSR, responses to 483s, and Warning Letters).
- Ms. Bierman has spoken and taught at medical device industry conferences on the fundamentals of medical device law. She also has written articles for domestic and international publications regarding medical device and pharmaceutical regulatory issues.
- Ms. Bierman is admitted to practice in the District of Columbia.

Biographies

Sharon A. Segal, Ph.D.
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- Sharon A. Segal, Ph.D. is the Director of Regulatory Science for the FDA/Product Regulation Practice. She provides scientific and regulatory consulting services to both domestic and international companies on FDA-regulated products.
- Dr. Segal has extensive experience in pharmacology, physiology and toxicology, and in developing and managing regulatory strategies, jurisdictional disputes, product development plans, preclinical and clinical testing programs, regulatory submissions, due diligence, and product defense strategies for medical devices, drugs, biologics, foods, and dietary supplements.
- Dr. Segal has given numerous presentations and moderated panel discussions at scientific and regulatory meetings both in the U.S. and abroad. She has published over 20 articles in areas such as the clinical testing of medical devices and the regulation of medical devices and biologics.

Agenda

- Navigating the FDA: Overview of review process
- Case studies:
  - Electrocardiogram
  - RF ablation device for treating hard tumors
  - Remote medication management system
  - Injectable hyaluronic acid for osteoarthritis
- Promotion

Navigating the FDA: Moving from Product Concept Through Agency Review and Clearance/Approval

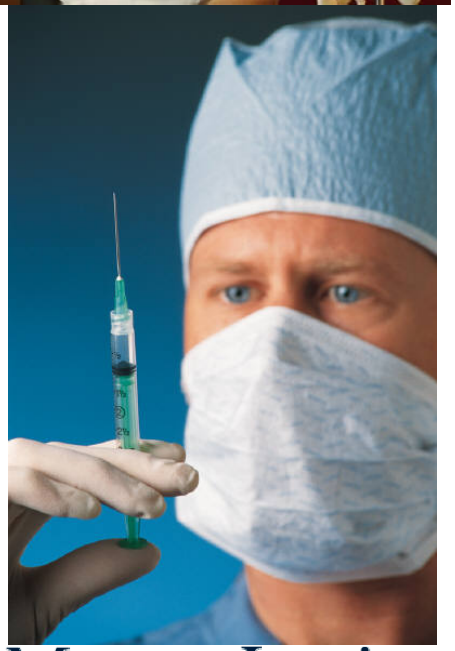
- Is my product a drug, device, biologic, or combination product?
- How will my device be regulated?
- What is the pathway to market?
- What data are required?
- If and when should I be interacting with FDA?
- What if I don't get the answer I want from FDA?
- What if I make changes to my device after market?
- What can I say about my device?

Is my product a drug, device, biologic, or combination product?

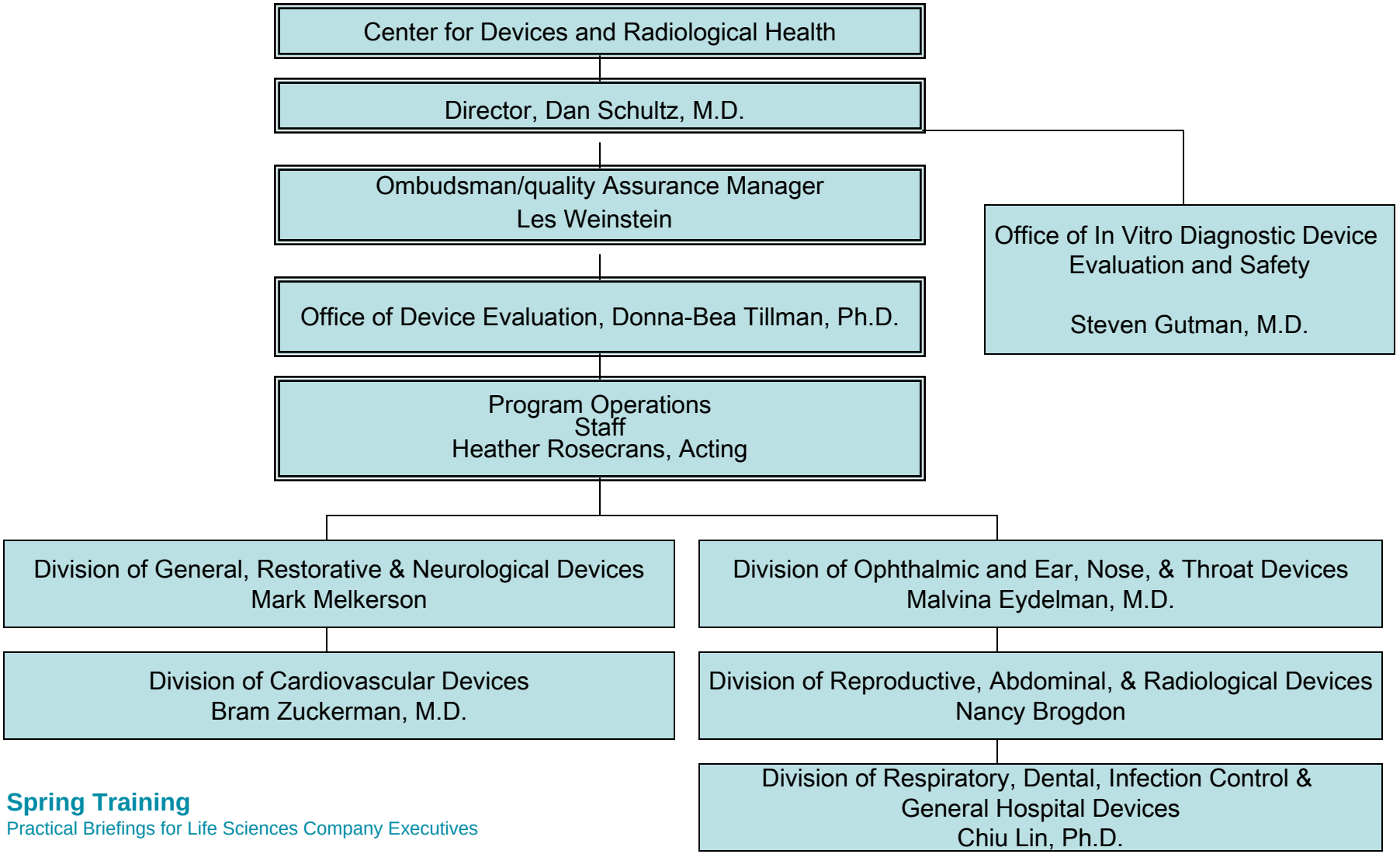
- Your product is a medical device if:
  - It is an instrument, apparatus, implement, machine, contrivance, implant, *in vitro* reagent, or other similar article;
  - It is intended for use in the diagnosis of disease or other conditions, or in the cure, treatment or prevention of disease, or intended to affect the structure or function of the body; and
  - It does not achieve its principal purpose by chemical action in or on the body or by being metabolized.

Is my product a drug, device, biologic, or combination product?

- A product's device status is not always obvious
  - Devices with biological properties:
    - *Collagen injections for aesthetic purposes*
    - *Orthobiologics for spinal fusion*
    - *Cellular-based wound management products*
  - Devices with drug properties:
    - *Hyaluronic acid (HA) injections for osteoarthritis: compare HA lung surfactant (drug)*
    - *CO_2 (medical gas) delivered to the lungs for sleep apnea - compare medical O_2 (drug)*
  - Stand-alone software products



How will my device be regulated?

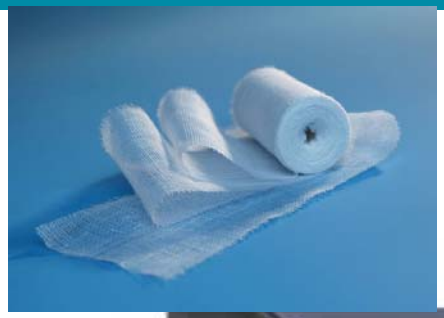


How will my device be regulated?

- The extent of FDA regulation applicable to a particular medical device or accessory depends on the *product classification*
- Device classification is determined by the *intended use* of the device
- FDA classifies medical devices based on risk:
  - Class I (lowest risk)
  - Class II, exempt or non-exempt (moderate risk)
  - Class III (highest risk)

How will my device be regulated?

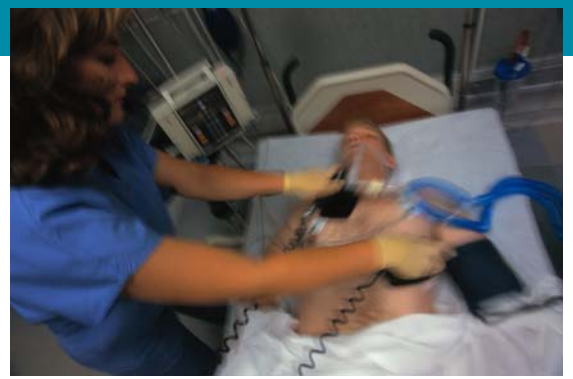
- Class I:
  - Examples:
    - *manual stethoscope, elastic bandages, otoscope, nasal stents*
  - Controls:
    - *General controls are sufficient to assure safety and effectiveness*
  - Premarket review:
    - *Generally exempt from premarket review*



How will my device be regulated?

- Class II:
  - Examples:
    - *Medical imaging software, ECG, pulse oximeters, blood glucose monitors*
  - Controls:
    - *General controls insufficient to assure safety and effectiveness*
    - *Sufficient information exists to establish special controls to provide such assurance (e.g., industry standards, guidance)*
  - Premarket review:
    - *Premarket notification 510(k) generally required (sometimes exempt)*

How will my device be regulated?



- Class III:
  - Examples:
    - *defibrillators, MRI, artificial hip joints, implants*
  - Includes:
    - *Products for use in supporting/sustaining human life, preventing impairment to human health, or unreasonable risk of illness or injury*
    - *Technology with important new questions of safety or efficacy (e.g., novel technology, novel indication)*
  - Controls:
    - *General/special controls insufficient to assure safety and effectiveness*
    - *Additional postmarketing requirements*
  - Premarket review:
    - *Premarket approval (PMA) based upon "reasonable assurance" of safety and effectiveness*

What is the pathway to market?

- 510(k) exempt
- 510(k)
- Combination product
- PMA

What is the pathway to market?
510(k) vs. PMA

- 510(k) if:
  - Substantial equivalence to legally marketed predicate devices can be demonstrated
  - Not high risk device
- PMA if:
  - General/special controls insufficient to assure safety and effectiveness
  - New technology/intended use
  - High risk devices
  - No legally marketed predicate devices

What is the pathway to market?
510(k)

- For Class I and II devices (unless exempt)
- Established in 1976; includes grandfathering provisions
- Over 90% of all devices are marketed via 510(k)s
- Fewer requirements than premarket approval
- Statutory 90-day process; often longer, depending upon whether questions are raised

What Devices Can a 510(k) Be Used For?

- Devices “substantially equivalent” to a predicate device
- Predicate devices are:
  - pre-Amendments (pre-1976) devices (documented evidence of status required)
  - legally marketed Class I or II devices
  - pre-Amendments Class III devices for which a Premarket Approval Application is not yet required
- Examples:
  - Rubella IVD - 135 previous 510(k)s
  - Catheter - 134 previous 510(k)s

Substantial Equivalence

FFDCA § 513(i)

The device has:

- Same intended use, and
- Same technological characteristics as the predicate device;

OR

- Same intended use, and
- Different technological characteristics from the predicate device

BUT

Substantial Equivalence

- The different technological characteristics do not raise new questions of safety and efficacy, and
- There are accepted scientific methods for evaluating whether safety and effectiveness have been adversely affected by the new technological characteristics, and
- There are data or information to demonstrate that safety or effectiveness have not diminished

- Conformance with voluntary standards can be used to demonstrate substantial equivalence

“Different Technological Characteristics”

- Could include changes in:
  - Materials (*e.g.*, catheter polymer material)
  - Design (*e.g.*, change in catheter diameter)
  - Energy sources (*e.g.*, manual vs. automated)
  - Principles of operation

What Are "New Questions of Safety and Efficacy"?

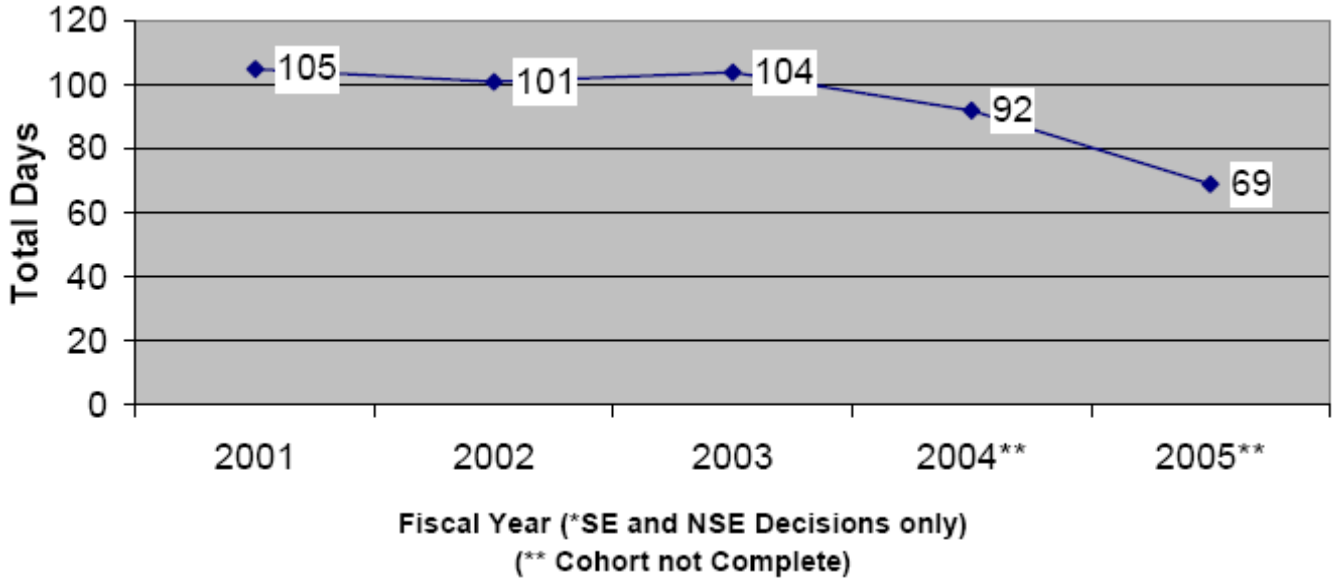
- Not defined in legislative history or guidance
- Provides FDA with substantial discretion
- Examples:
  - IVD
    - *Radiolabeled antibodies (RIA) vs. Enzyme-linked antibodies (ELISA)*
  - Catheter
    - *Immunological reaction to new polymer material*

What Must a 510(k) Include?

- Identification
- Table of contents
- Truthful and Accurate Statement
- Indications for use
- Device name
- Establishment registration number
- Classification
- Performance standards
- Labeling
- Description of device
- Substantial equivalence comparison
- Performance/clinical data sometimes required
- 510(k) summary or statement (807.92, 93)
- Class III certification and summary (when appropriate) (807.94)

Be realistic about time goals

Average Total Time Elapsed to 510(k) Final Decision



What is the pathway to market?
PMA

- For Class III :
  - new technology or intended use
  - not substantially equivalent devices
  - pre-1976 high risk devices
  - used in supporting/sustaining human life, preventing impairment to human health, or unreasonable risk of illness or injury
- PMA requires “reasonable assurance” of device safety and effectiveness; generally one or more prospective, adequately controlled, clinical trials

What Must a PMA Include?

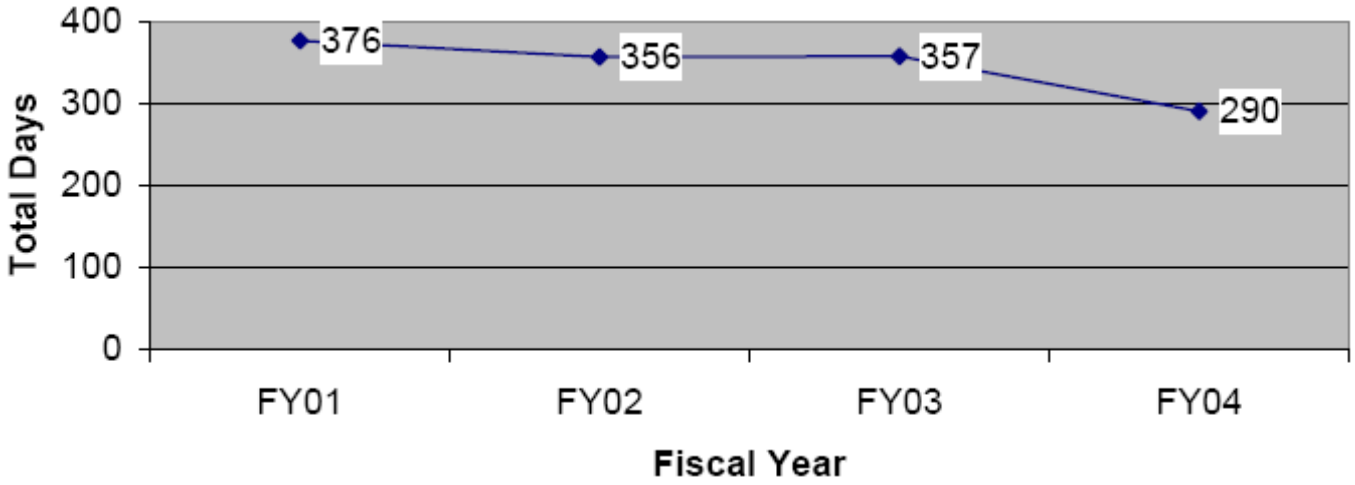
- Indications for use
- Complete device description
- Marketing history
- Summary of preclinical and clinical studies and conclusions
- Complete study reports and data listings
- Manufacturing information
- Relevant published studies
- Labeling
- Summary of Safety and Effectiveness

Other PMA Requirements/Activities

- Expert Advisory Panel review for most original PMAs
- Additional post-marketing requirements
  - Continuation/expansion of pivotal study
  - Postapproval study
  - Physician training/education
  - Focus groups
  - Tracking

Be realistic about time goals

Average Total Elapsed Time for PMAs and Panel Track PMA Supplements



What is the pathway to market?
Combination Product

- Two or more regulated components, that are physically, chemically, or otherwise combined or mixed and produced as a single entity
- Two or more separate regulated products packaged together in a single package or as a unit

What is the pathway to market?
Combination Product

- Investigational or approved product packaged separately that is intended for use only with an approved individually specified product where both are required to achieve the intended use
- Any investigational drug, device, or biological product packaged separately for use only with another individually specified investigational product where both are required to achieve the intended use

What is the pathway to market?
Combination Product

The components are physically, chemically or otherwise combined:

- Drug – Biologic Combinations:
  - *Monoclonal antibody combined with a therapeutic drug*
  - *Biologic combined with radiopharmaceutical*
- Device coated or impregnated with a drug or biologic:
  - *Drug-eluting stent or disk*
  - *Condom with spermicidal coating*
  - *Skin substitutes with cellular components*
  - *Orthopedic implant with growth factors*
- Prefilled drug or biologic delivery device:
  - *Insulin, epinephrine or interferon injector pens*
  - *Transdermal patches*

What is the pathway to market?
Combination Product

- Sponsor may submit a Request for Designation ("RFD") to the Office of Combination Products to determine which FDA Center will have primary jurisdiction over the combination product
- When: before filing any application for premarket review
- Letter of designation issued within 60 days of filing date
- Binding effect of letter of designation -- cannot change designation without sponsor's consent, except "to protect the public health or for other compelling reasons"

When clinical data are required: Investigational Devices

- Clinical Trials Investigational Device Exemption (IDE)
  - FDA oversight of conduct of study, use of device, protection of human subjects
  - FDA review depends upon determination of Significant Risk (SR) or Nonsignificant Risk (NSR) Device
  - Determination made by sponsor, then IRB; FDA oversight
  - Investigation may begin 30 days after receipt of IDE, unless FDA notifies sponsor otherwise

When clinical data are required:
IDE Data Requirements

- Investigational plan
- Report of prior investigations (preclinical, clinical)
- Manufacturing information
- IRB actions
- Investigator agreements
- Informed consent form
- Device labeling
- Cost of device

What is the pathway to market?

Explore all pathway options

- For 510(k)s:
  - Third party review; special 510(k)s; abbreviated 510(k)s
  - Classification options (e.g., informal up-the-chain; *de novo* downclassification; more formal petition)
  - Pre-meetings(s); informal discussions
- For PMAs:
  - Early collaboration meetings
  - Modular review; real-time labeling review
  - Literature-based supplements; expedited supplements
  - PDPs; expedited PMAs

If and when should I be interacting with FDA?

- Informal interactions
- Pre-IDE meetings
- Agreement meetings
- Strategies for addressing scientific disputes
- Preparing for panel meetings

What are other pathway considerations?

- Establishment registration/device listing
- MDRs/recalls
- Design control/QSR
- Reimbursement
- Unconvincing results and/or new data concerns
- Meaningful clearance or approval
- Competitive pipeline issues
- Medical community acceptance and other market dynamics.

What if I don’t get the answer I want from FDA?

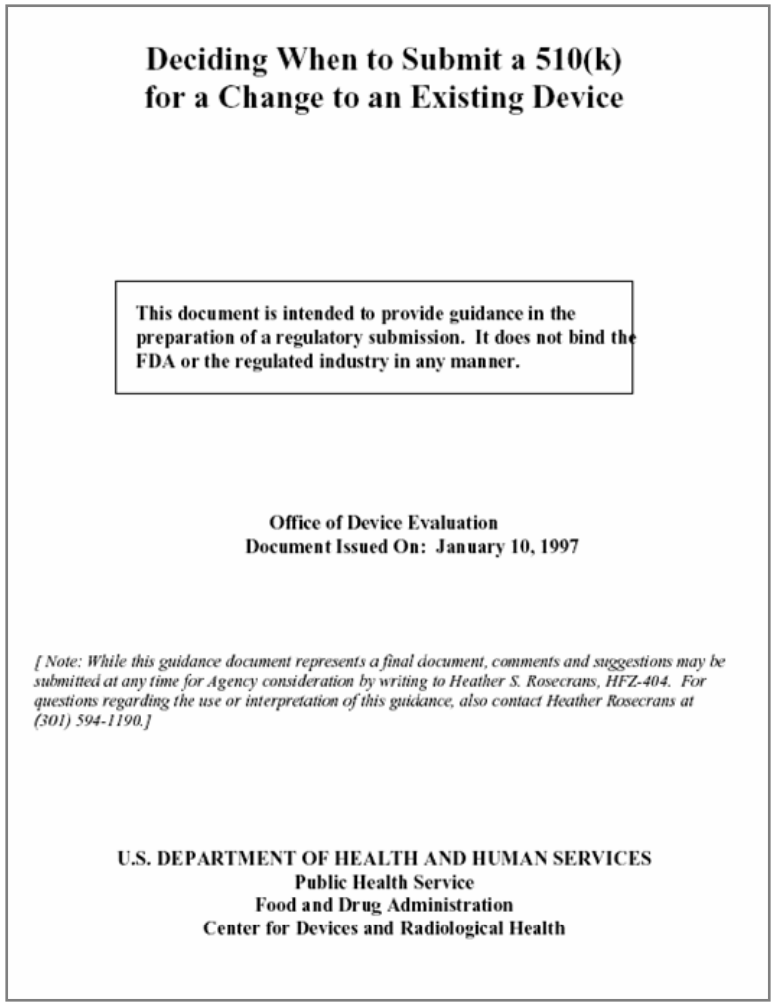
- Know when and how to pick your battle
  - Informal up-the-chain review
  - Mediation by CDRH Ombudsman
  - Medical Devices Dispute Resolution Panel
  - HHS
  - Congress

What if I make changes to my device after clearance/approval?
510(k)

- Consider all postmarket device changes:
  - Change due to recall/corrective action
  - Labeling change (indications, warnings/ precautions, reuse, home or OTC use)
  - Technology or performance change (performance specifications, operating principle, sterilization)
  - Materials change (type, supplier, formulation)
- Assess need for 510(k) -- FDA Guidance Document
- 510(k) or memo to file

What if I make changes to my device after clearance/approval?
510(k)

- CDRH Guidance
  - Decision trees
  - Flowcharts



Deciding When to Submit a 510(k) for a Change to an Existing Device

This document is intended to provide guidance in the preparation of a regulatory submission. It does not bind the FDA or the regulated industry in any manner.

Office of Device Evaluation
Document Issued On: January 10, 1997

[Note: While this guidance document represents a final document, comments and suggestions may be submitted at any time for Agency consideration by writing to Heather S. Rosecrans, HFZ-404. For questions regarding the use or interpretation of this guidance, also contact Heather Rosecrans at (301) 594-1190.]

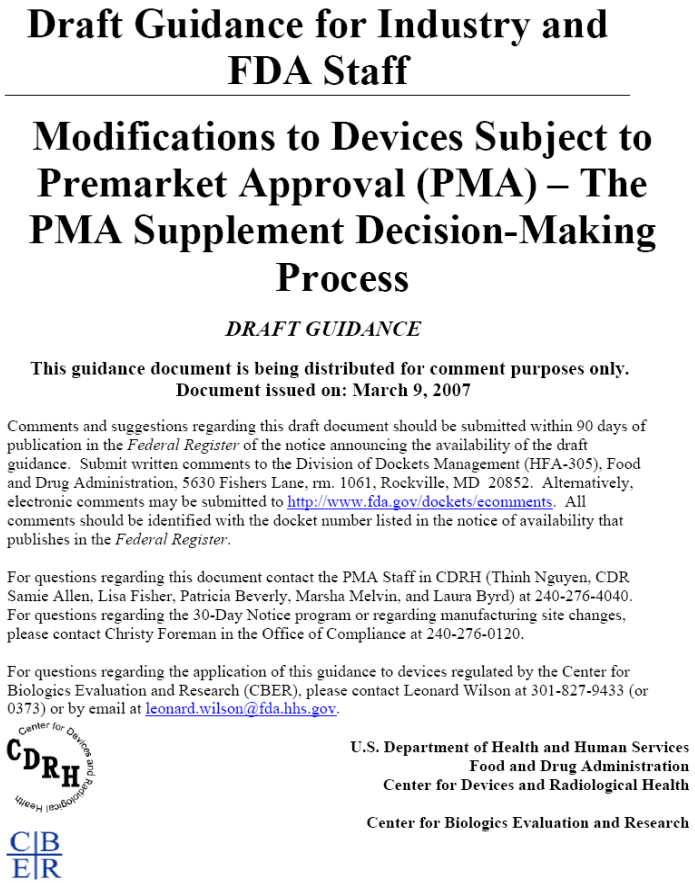
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health

What if I make changes to my device after clearance/approval?
PMA

- Changes affecting safety or effectiveness:
  - New indications for use
  - Labeling changes
  - Use of a different facility or establishment to manufacture, process or package
  - Changes in sterilization procedures
  - Changes in packaging
  - Changes in the performance or design specifications, circuits, components, ingredients, principle of operation, or physical layout

What if I make changes to my device after clearance/approval?
PMA

- CDRH Guidance
  - Decision trees
  - Flowcharts



Draft Guidance for Industry and FDA Staff

Modifications to Devices Subject to Premarket Approval (PMA) – The PMA Supplement Decision-Making Process

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.
Document issued on: March 9, 2007

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Alternatively, electronic comments may be submitted to http://www.fda.gov/dockets/ecomments. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this document contact the PMA Staff in CDRH (Thinh Nguyen, CDR Samie Allen, Lisa Fisher, Patricia Beverly, Marsha Melvin, and Laura Byrd) at 240-276-4040. For questions regarding the 30-Day Notice program or regarding manufacturing site changes, please contact Christy Foreman in the Office of Compliance at 240-276-0120.

For questions regarding the application of this guidance to devices regulated by the Center for Biologics Evaluation and Research (CBER), please contact Leonard Wilson at 301-827-9433 (or 0373) or by email at leonard.wilson@fda.hhs.gov.

CDRH Center for Devices and Radiological Health

CBER

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Center for Biologics Evaluation and Research

Case Studies

Product A
Electrocardiogram

- Is my product a drug, device, biologic, or combination product?
- How will my device be regulated?
- What is the pathway to market?
- What data are required?

Product B
RF Ablation Device for Treating Hard Tumors

- Is my product a drug, device, biologic, or combination product?
- How will my device be regulated?
- What is the pathway to market?
- What data are required?

Product C
Remote Medication Management System

- Is my product a drug, device, biologic, or combination product?
- How will my device be regulated?
- What is the pathway to market?
- What data are required?

Product D
Injectable Hyaluronic Acid for Osteoarthritis

- Is my product a drug, device, biologic, or combination product?
- How will my device be regulated?
- What is the pathway to market?
- What data are required?

Product E
Drug Eluting Stent

- Is my product a drug, device, biologic, or combination product?
- How will my device be regulated?
- What is the pathway to market?
- What data are required?

What can I say about my device?

- Before FDA approval/clearance
- Pending FDA approval/clearance
- After FDA approval/clearance

Before FDA Clearance/Approval: Labeling

Investigational device labeling:

- Must be labeled: “CAUTION—Investigational device. Limited by Federal law to investigational use”
- Cannot be false or misleading
- Cannot represent that device is safe or effective (i.e., that it safely and effectively performs the function for which FDA approval/clearance is being sought)

Before FDA Clearance/Approval: Promotion

Investigational device promotion:

- Cannot promote or test market an investigational device
- Cannot commercialize investigational device by charging more than necessary to recover costs
- Cannot unduly prolong investigation
- Cannot represent that an investigational device is safe or effective

Before FDA Clearance/Approval: Promotional Safe Harbors

- Unsolicited requests
- Continuing medical education
- Recruitment of investigators/study subjects
- Scientific exchange (*e.g.*, medical meetings)
- Devices authorized for sale in other countries

Pending FDA Clearance: Labeling and Promotion

- Promotion/display of pending 510(k) devices -- Permitted under certain circumstances:
  - Must be labeled "Pending 510(k) clearance -- Not available for sale in the U.S."
  - Must not be a device covered by an existing Investigational Device Exemption
  - Pending 510(k) must not represent a new intended use of an existing marketed device
  - May not take orders or be prepared to take orders

FDA, Compliance Policy Guide 7124.19 (Sept. 24, 1987)

After FDA Clearance/Approval: Labeling

- Label: Upon the immediate article (21 U.S.C. § 321(k)
- Labeling: Broadly defined: Upon the article or accompanying the article (21 U.S.C. § 321(m)). Can include brochures, mailings, press releases, detail pieces, "home-made" sales materials, literature, reprints, website, videos, testimonials, investor relations materials
- *See* 21 C.F.R. Part 801

After FDA Clearance/Approval: Labeling and Promotion

- Labeling and promotional materials:
  - May not be false or misleading
  - Must be consistent with clearance or approval
  - Comparative/superiority claims generally must be substantiated by “head to head” clinical trials and statistically significant differences
  - May not include any representation that creates impression of official approval of device because of 510(k) clearance (e.g., “FDA approved”) (21 C.F.R. § 807.97)

Thank You!

- Questions and Discussion

BACK-UP

When are data required?
510(k)

- To demonstrate that device is as safe and effective as predicate when there are different technological characteristics / different materials
- To demonstrate that device does not raise new questions of safety and efficacy when there are different technological characteristics
- To demonstrate that device performs as intended
- If required by device-specific guidance

BUT

- "Least Burdensome" themes should be considered

What data are required?
510(k)

- Compare to predicate device: technological characteristics, intended use, performance specifications
- Bench / performance testing
- Biocompatibility testing
- Use of standardized tests (ASTM, etc.)
- Animal data -- sometimes (new indication, novel design features)
- Clinical data --increasingly more often (new uses, novel design features, new materials)
- Specific FDA guidance documents address certain product categories

What data are required?
PMA

- Manufacturing (21 C.F.R. Part 820)
- Biocompatibility testing (ISO 10993)
- Bench/performance testing
- Animal testing (other than biocompatibility)
- Clinical testing (1 pivotal trial)