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Classification and the Essentials of the Device Premarket Review Process

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Overview

- What is a Device?
- Device Classification
- Requesting Classification under Sec. 513(g) of the Act
- Reclassification and the 515 Program Initiative
- Premarket Notification under Sec. 510(k) of the Act [510(k)]
- *De Novo* Submission
- Premarket Approval (PMA)
- Investigational Device Exemption (IDE)

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Definition of a “Device”

Sec. 201(h) of the Act defines a device as:

an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is

1. recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them,
2. intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
3. intended to affect the structure or function of the body, and which does not achieve its primary intended purposes through chemical action within or on the body and is not dependent upon being metabolized to achieve its primary intended purposes

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Device Classification

Medical devices are placed into three classes based on risk:

- Class I: subject only to "general controls," and
  1. general controls are sufficient to provide reasonable assurance of the safety and effectiveness of the device, or
  2. if there is not enough information to determine that general controls are sufficient, the device is not life-supporting or life-sustaining or for a use which is of substantial importance in preventing impairment of human health, and which does not present a potential unreasonable risk of illness of injury

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General Controls

- The controls authorized under the following sections of the Federal Food, Drug and Cosmetic Act:
  - Sec. 501 (adulteration),
  - Sec. 502 (misbranding),
  - Sec. 510 (registration),
  - Sec. 516 (banned devices),
  - Sec. 518 (notification and other remedies),
  - Sec. 519 (records and reports), and
  - Sec. 520 (general provisions)
- Exemptions may be obtained for certain general controls:
  - Sec. 510 (registration, product listing and premarket notification),
  - Sec. 519 (records and reports), and
  - Sec. 520(f) (good manufacturing practice requirements of the quality system regulation)

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Device Classification (cont.)

Medical devices are placed into three classes based on risk:

- Class II: subject to general and "special controls," and
  - general controls alone are insufficient to provide reasonable assurance of safety and effectiveness, and
  - there is sufficient information to establish special controls
- Class III: requires "premarket approval," and
  - the device is life-supporting or life-sustaining, or for a use which is of substantial importance in preventing impairment of human health, or if the device presents a potential unreasonable risk of illness or injury, and
  - insufficient information exists to determine that general controls and/or special controls are sufficient to provide reasonable assurance of safety and effectiveness

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Special Controls

- Special controls include:
  - performance standards,
  - postmarket surveillance,
  - patient registries,
  - development and dissemination of guidance documents (including guidance on the submission of clinical data in premarket notification submissions in accordance with section 510(k) of the act),
  - recommendations, and
  - other appropriate actions as the Commissioner deems necessary to provide such assurance
- Note that special controls that closely mirror the controls established under premarket approval are generally not appropriate

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Sec. 513(g) Requests for Classification Information

- A 513(g) request is “a request made under section 513(g) for information respecting the class in which a device has been classified or the requirements applicable to a device”
- FDA’s response to a 513(g) request will provide information regarding device classification and/or applicable regulatory requirements (such as the appropriate marketing submission)
- A user fee is required to process the request

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Reclassification

- The original classification of a group of devices can be adjusted
- FDA may, on its own, or in response to an outside petition, change a device's classification by administrative order
- Reclassifying a device to a lower class requires convincing the FDA that the less stringent class requirements will be sufficient to provide “a reasonable assurance of safety and effectiveness”
- Reclassification of a device by administrative order requires:
  - Publication of a proposed order in the Federal Register,
  - A meeting of a device classification panel, and
  - Consideration of comments from all affected stakeholders, including patients, payors, and providers

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515 Program Initiative

- Classification decisions may result in “upclassification” in certain circumstances
- When the medical device regulation program began in the late 1970s, there were over 100 Class III device types that could be marketed through a 510(k) notification
- This was intended to be temporary, such that over time these device types would either be reclassified into Class I or II, or that FDA would maintain the classification in Class III and call for PMA applications
- The FDA is currently reviewing the remaining 510(k) Class III device types to make a determination on the appropriate classification

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Premarket Notification under Sec. 510(k)

- A 510(k) is a premarket submission made to FDA to demonstrate that the device to be marketed is at least as safe and effective (or "substantially equivalent") to one or more legally marketed devices (or "predicates")
- Eligible predicates are:
  - A device that was legally marketed prior to May 28, 1976 (a "preamendments device") for which a PMA is not required,
  - A device which has been reclassified from Class III to Class II or I, or
  - A device which has been found substantially equivalent through the 510(k) process
- Payment of a user fee is required for FDA review of a 510(k)

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New 510(k) Guidance

- On July 28, 2014, FDA issued the final guidance "The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications"
- The guidance addresses, among other things:
  - multiple predicates;
  - whether a new device with new indications for use has a new "intended use"; and
  - whether different technological characteristics raise different questions of safety and effectiveness.

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Split Predicates

- Section 513(i) of the FD&C Act and 21 CFR 807.100(b) states that substantial equivalence requires:
  - same intended use as the predicate device, and
  - technological characteristics that are:
    - the same, or
    - different but do not raise different questions of safety and effectiveness
- According to FDA, “split predicates” are inconsistent with the 510(k) regulatory standard:
  - Demonstrating that a new device has the same intended use as one marketed device, while
  - Comparing the new device’s technological characteristics with a second marketed device that has a different intended use

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Multiple Predicate Devices

- A manufacturer may use multiple predicate devices to help demonstrate substantial equivalence in certain circumstances:
  - When combining features from two or more predicate devices with the same intended use into a single new device,
  - When seeking to market a device with more than one intended use, or
  - When seeking more than one indication for use under the same intended use.

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Types of 510(k) Submissions

- Each submission must include the required elements identified in 21 CFR 807.87, but they differ in how substantial equivalence is established:
- Traditional 510(k)
  - Uses data that directly compares the new device to the predicate to establish substantial equivalence
- Abbreviated 510(k)
  - Relies on the use of guidance documents, special controls, and recognized standards to establish substantial equivalence

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Types of 510(k) Submissions (cont.)

- Special 510(k)
  - Relies on conformity to design controls (21 C.F.R. 820.30) to establish substantial equivalence of a modification to the submitter's own predicate device
  - The FDA has committed to review Special 510(k)s within 30 days of receipt, as opposed to the 90 day timeframe for Traditional and Abbreviated 510(k)s
  - Special 510(k)s are only appropriate where the modification does not:
    1. affect the intended use or
    2. alter the fundamental scientific technology of the device

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510(k) Device Modifications

- Due to complaints by industry, Congress mandated FDA withdraw its recent draft guidance “510(k) Device Modifications: Deciding When to Submit a 510(k) for a Change to an Existing Device”
- For now, the 1997 guidance “Deciding When to Submit a 510(k) for a Change to an Existing Device (K97-1)” is still in effect
- Guidance provides flowcharts for different types of changes, and is primarily focused on:
  - Does the change affect the indications for use?
  - Are clinical data necessary to evaluate safety and effectiveness for purposes of determining substantial equivalence?
  - Do results of design validation raise new issues of safety and effectiveness?

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De Novo Process

- Essentially a combination of a 510(k) submission with a downclassification petition
- Used when a new device is not substantially equivalent to any pre-existing product, but the automatic inclusion in Class III is not appropriate because the product does not pose a significant safety risk
- If the FDA determines that reclassification is not appropriate, the device will require PMA approval before marketing can commence

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De Novo Process (cont.)

- Steps required with the *De Novo* process:
  - Option 1:
    - Submission of a 510(k) claiming substantial equivalence to a predicate,
    - Issuance of a "not substantially equivalent" (NSE) decision by FDA,
    - Submission of a request for *de novo* classification within 30 days of the NSE decision proposing general and/or special controls that should be applied to the new device
  - Option 2:
    - Submission of a request for *de novo* classification without 510(k)
    - This is subject to FDA not identifying a legally marketed device that may reasonably be the basis for review of substantial equivalence
  - FDA's decision on classification must be made within 120 days
  - If successfully classified, the new device may serve as a predicate for other 510(k) submissions

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Premarket Approval (PMA)

- Approval of a PMA application requires a determination by FDA that the PMA contains sufficient valid scientific evidence to provide reasonable assurance that the device is safe and effective for its intended use(s)
- "Reasonable assurance" is a lower standard than the "substantial evidence" required for drugs
- Valid scientific evidence is principally drawn from well-controlled investigations, but may also include:
  - partially controlled studies,
  - studies and objective trials without matched controls,
  - well-documented case histories conducted by qualified experts, and
  - reports of significant human experience with a marketed device

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Premarket Approval (cont.)

- Requires payment of a user fee for FDA review
- Requires significantly more detailed information than what is provided in a 510(k), particularly with respect to:
  - labeling and advertising
  - manufacturing and quality controls
- As with 510(k)s, there are different PMA types:
  - Traditional PMA
  - Modular PMA (done in pieces)
  - Streamlined PMA (comparable to an Abbreviated 510(k))
  - Product Development Process (combines aspects of an IDE with a PMA)
  - Humanitarian Device Exemption (for orphan devices, provides an exemption from having to establish device effectiveness)
  - Note that non-Traditional PMAs are only infrequently used

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Investigational Device Exemption (IDE)

- Permits the human clinical testing of a device in the U.S.
- Two different requirements based on risk:
  - Significant Risk Device Study involves a device that presents a potential for serious risk to the health, safety, or welfare of a subject, such as:
    - Implants,
    - Devices used for supporting or sustaining human life, or
    - Devices that are of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health
  - Nonsignificant Risk Device Study involves any other type of device

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Investigational Device Exemption (cont.)

- Significant Risk Device Studies require both FDA and IRB approval
- Nonsignificant Risk Device Studies require only IRB approval, and have reduced recordkeeping and reporting requirements
- Note that an IDE is not required to conduct a study outside of the U.S., but may be useful in determining the suitability of the design of clinical trials and for obtaining permission to export investigational devices out of the U.S.

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Exceptions Applicable to *In Vitro* Diagnostic Products

- Research Use Only (RUO): products that are in the laboratory research phase of development (either basic research or the initial search for potential clinical utility)
- RUO products may not be represented as an effective *in vitro* diagnostic product, and must be labeled "For Research Use Only. Not for use in diagnostic procedures."
- Investigational Use Only (IUO): products that are in the clinical investigation phase of development
- If the device is exempt from IDE requirements, it cannot be used for human clinical diagnosis unless the diagnosis is being confirmed by another, medically-established diagnostic product or procedure
- IUO products must be labeled "For Investigational Use Only. The performance characteristics of this product have not been established."

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Least Burdensome Provisions

- Congress recently strengthened the Least Burdensome Provisions in FDASIA
- Clinical data demonstrating a reasonable assurance of device effectiveness is data "necessary to establish device effectiveness," which is "the minimum required information that would support . . . reasonable assurance of effectiveness"
  - FDA is to "consider . . . the least burdensome appropriate means of evaluating device effectiveness that would have a reasonable likelihood of resulting in approval."
- Information demonstrating that devices with differing technological characteristics are substantially equivalent is limited to "information that is necessary to making substantial equivalence determinations," which is "the minimum required information that would support . . . substantial equivalence"
  - FDA is to "consider the least burdensome means of demonstrating substantial equivalence"

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Pre-Submission Program

- The Pre-Submission Program is a way for sponsors to obtain early, informal input on an aspect of a future IDE, 510(k) or PMA application
- FDA is not bound by the input it provides as part of the Pre-Submission, unless it is provided in an Early Collaboration Meeting (Determination or Agreement)
- It is useful in three contexts (among others):
  - Non-Significant Risk Studies: Obtain ODE input on the design of a nonsignificant risk study or the development of the clinical protocol, and/or the statistical plan before the nonsignificant risk study is conducted
  - On-going Pre-clinical Testing: When the IDE sponsor is still conducting bench/animal testing and would like Agency feedback on a clinical protocol or 510(k) submission
  - During Development of the Clinical Protocol: Obtain guidance on the bench/animal testing needed before it is conducted to increase the likelihood that the testing will support initiation of the clinical study

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QUESTIONS?

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Post-Market Requirements and Concerns for Medical Devices

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Overview

- Establishment Registration and Device Listing (21 C.F.R. Part 807)
- Quality System Regulation (21 C.F.R. Part 820)
- Medical Device Reporting (21 C.F.R. Part 803)
- Reports of Corrections and Removals (21 C.F.R. Part 806)
- Other Post-Market Requirements
  - Device tracking
  - 522 Postmarket Surveillance Studies

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Establishment Registration and Device Listing

- Establishments involved in the production and distribution of medical devices in the U.S. are required to register annually with the FDA
- Most registered establishments must list the devices and the activities performed at that establishment, and pay an annual establishment registration user fee
- Registration and listing does not constitute accreditation or certification by the FDA, or address issues regarding the qualifications of the establishment or the quality of its devices

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U.S. Facilities Required to Register and List

- Manufacturers of devices (including custom devices and export only devices)
- Manufacturers of accessories/components packaged for commercial distribution to end users
- Kit assemblers
- Relabelers, repackagers and remanufacturers (no fee required)
- Reprocessors of single use devices
- Contract manufacturers and sterilizers who commercially distribute finished devices for the hiring firm
- Specification developers and facilities that maintain complaint files
- Initial distributor / importer (registration only)

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Foreign Facilities Required to Register and List

- Manufacturers of devices (including custom devices)
- Foreign exporters of devices located in a foreign country (no fee required)
- Kit assemblers
- Relabelers, repackagers and remanufacturers (no fee required)
- Reprocessors of single use devices
- Contract manufacturers and sterilizers whose devices are shipped to U.S. by the facility or by any other firm
- Specification developers and facilities that maintain complaint files

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Facilities Not Required to Register and List

- Manufacturer of components that are distributed only to a finished device manufacturer
- Domestic distributors (other than the initial distributor / importer)
- Specification consultants
- Manufacturers of devices being investigated under an Investigational Device Exemption (IDE)

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Quality System Regulation (QSR)

- 21 C.F.R. Part 820 establishes the basic current good manufacturing practice (cGMP) requirements applicable to manufacturers of finished medical devices
- Harmonized with international, industry-accepted standards for the control and management of manufacturing and quality control testing
- Relies upon written procedures, documentation and review as key methods to manage manufacturing and quality operations
- Quality control testing takes the form of verification and/or validation

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QSR Terminology

- *Verification:* confirmation by examination and provision of objective evidence that specified requirements **have been** fulfilled
- *Validation:* confirmation by examination and provision of objective evidence that the particular requirements for a specific intended use **can be consistently** fulfilled

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Elements of the Quality System Regulation

- Subpart A--General Provisions
  - § 820.1 - Scope
  - § 820.3 - Definitions
  - § 820.5 - Quality system
- Subpart B--Quality System Requirements
  - § 820.20 - Management responsibility
  - § 820.22 - Quality audit
  - § 820.25 - Personnel
- Subpart C--Design Controls (§ 820.30 - Design controls)
- Subpart D--Document Controls (§ 820.40 - Document controls)

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Elements of the Quality System Regulation

- Subpart E--Purchasing Controls (§ 820.50 - Purchasing controls)
- Subpart F--Identification and Traceability (§ 820.60 - Identification and § 820.65 - Traceability)
- Subpart G--Production and Process Controls
  - § 820.70 - Production and process controls
  - § 820.72 - Inspection, measuring, and test equipment
  - § 820.75 - Process validation
- Subpart H--Acceptance Activities
  - § 820.80 - Receiving, in-process, and finished device acceptance.
  - § 820.86 - Acceptance status.

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Elements of the Quality System Regulation

- Subpart I--Nonconforming Product (§ 820.90 - Nonconforming product)
- Subpart J--Corrective and Preventive Action (§ 820.100 - Corrective and preventive action)
- Subpart K--Labeling and Packaging Control (§ 820.120 - Device labeling and § 820.130 - Device packaging)
- Subpart L--Handling, Storage, Distribution, and Installation
  - § 820.140 – Handling
  - § 820.150 – Storage
  - § 820.160 – Distribution
  - § 820.170 - Installation

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Elements of the Quality System Regulation

- Subpart M--Records
  - § 820.180 - General requirements
  - § 820.181 - Device master record
  - § 820.184 - Device history record
  - § 820.186 - Quality system record
  - § 820.198 - Complaint files
- Subpart N--Servicing (§ 820.200 - Servicing)
- Subpart O--Statistical Techniques (§ 820.250 - Statistical techniques)

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QSR Terminology

- The sum of the control and management operations is called the Quality System, with the primary QSR document called the Quality Policy
  - *Quality Policy:* The overall intentions and direction of an organization with respect to quality, as established by management with executive responsibility
  - *Quality System:* The organizational structure, responsibilities, procedures, processes, and resources for implementing quality management
  - *Management with executive responsibility:* Those senior employees of a manufacturer who have the authority to establish or make changes to the manufacturer's quality policy and quality system

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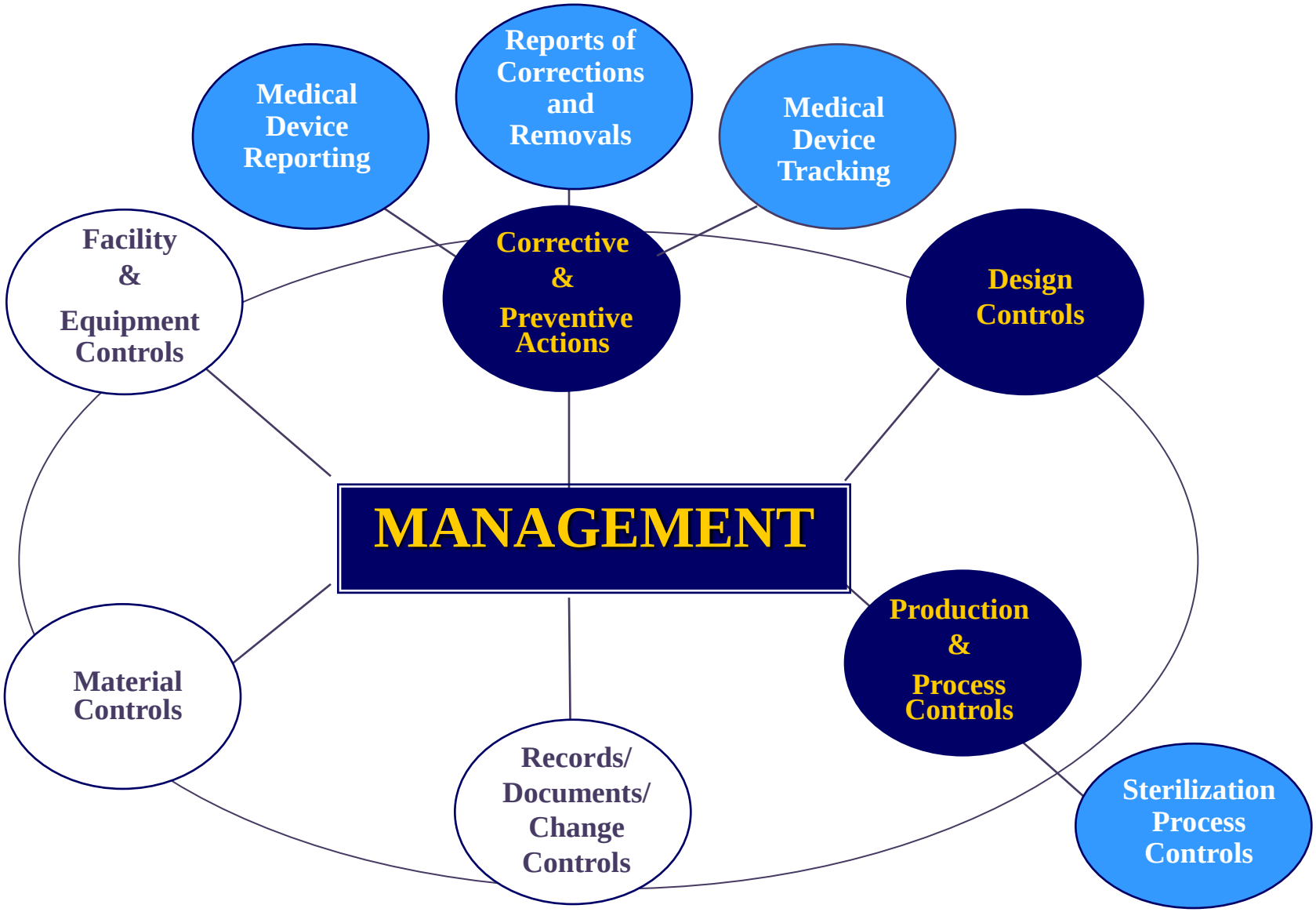
The Quality System

- The Quality System is grouped into seven subsystems
- Four subsystems are considered major and are the basic foundation of a firm's quality management system:
  - Management Controls
  - Design Controls
  - Production and Process Controls (P&PC)
  - Corrective and Preventive Actions (CAPA)
- The three remaining subsystems cut across a firm's quality management system and are evaluated while covering the four major subsystems:
  - Facilities and Equipment Controls
  - Materials Controls and
  - Document/Records/Change Controls


Medical Device Reporting
Reports of Corrections and Removals
Medical Device Tracking
Facility & Equipment Controls
Corrective & Preventive Actions
Design Controls
MANAGEMENT
Material Controls
Records/ Documents/ Change Controls
Production & Process Controls
Sterilization Process Controls

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Management Controls

- Quality Policy and objectives
- Quality System procedures and instructions
- Organizational structure with adequate resources for quality
- “Management Representative” responsible for establishing the Quality System and reporting on quality to management with executive responsibility
- Regular Quality Audits and Management Reviews
- Personnel with the appropriate education, training and experience
- Formal training program

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Audits and Reviews

- Management Review
  - A review of the suitability and effectiveness of the quality system by management with executive responsibility
  - Conducted at defined intervals (no longer than a year) and with sufficient frequency
  - The goal is to ensure that the quality system satisfies FDA requirements and the manufacturer's established quality policy and objectives

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Audits and Reviews (cont.)

- Quality Audit
  - Assure the compliance and effectiveness of the quality system
  - Conducted by individuals without direct responsibility for the matters being audited (consultants)
  - Observations should be corrected where necessary, according to the CAPA requirements
  - FDA will generally not review audit reports, however, FDA will review CAPAs taken as the result of a Quality Audit. Be sure to appropriately segregate the results of quality audits from CAPAs

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Corrective and Preventive Actions (CAPA)

- CAPA system is designed to proactively (preventative actions) and retroactively (corrective actions) address problems with the quality system

- CAPA process has seven (7) steps:
  1. Analyze quality data, using statistical methodology, where necessary, to identify quality problem(s);
  2. Investigate the cause of quality problem(s);
  3. Identify action(s) needed to correct and prevent recurrence of quality problem(s);

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Corrective and Preventive Actions (CAPA)
(cont.)

- CAPA process has seven (7) steps:
  4. Verify or validate action(s) taken to ensure effectiveness, and absence of an adverse impact on finished devices;
  5. Implement and record changes in methods and procedures as part of action(s) taken;
  6. Disseminate information regarding action(s) taken to those directly responsible for preventing quality problem(s); and
  7. Submit information on quality problem(s) and action(s) taken for management review

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Design Controls

- New designs require applying the following controls:

1. Design and development planning
   - plans that describe or reference the design and development activities and define responsibility for implementation
2. Design input
   - design requirements of the product that are appropriate and address the intended use of the product, including the needs of the user
   - Design inputs can also include requirements from specifications

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Design Controls

- New designs require applying the following controls:
  3. Design output
     - the results of a design effort that are essential for the proper functioning of the device and establish that the design conforms to design input requirements
  4. Design review
     - documented, comprehensive, systematic examination of a design to evaluate the adequacy of the design requirements, to evaluate the capability of the design to meet these requirements, and to identify problems
  5. Design verification
     - confirmation that the design output meets the design input requirements

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Design Controls

- New designs require applying the following controls:
  6. Design validation
     - performed under defined operating conditions on initial production units, lots, or batches, or their equivalents to ensure that devices conform to defined user needs and intended uses and includes testing of production units under actual or simulated use conditions
  7. Design transfer
     - ensure that the device design is correctly translated into production specifications
- Design history file
  - Contains or references the records necessary to demonstrate that the design was developed in accordance with the approved design plan and the design control requirements

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Medical Device Reporting (MDR)

- 21 C.F.R. Part 803 requires manufacturers to file a report with the FDA after becoming aware of an **MDR reportable event**
- An MDR reportable event is one where a device
  - May have *caused or contributed* to a death or **serious injury**
  - Has malfunctioned where, if the malfunction were to recur, it would be *likely* to cause or contribute to a death or **serious injury**
- A serious injury is an injury or illness that necessitates medical or surgical intervention to preclude permanent impairment of a bodily function or permanent damage to a body structure

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MDR Requirements

- The likelihood that a malfunction will cause or contribute to a death or serious injury *does not* include the chance that a malfunction will recur
  - FDA: The fact that the malfunction occurred once leads to the presumption that the malfunction will recur
- Reports are not required when information would cause a person qualified to make a medical judgment (i.e., physician, risk manager, biomedical engineer) to reach a reasonable conclusion that a device did not cause or contribute to an MDR reportable event
- Manufacturers are otherwise required to report MDRs involving:
  - Biased information
  - Incomplete information
  - User error

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MDR Requirements

- All manufacturers must have written MDR procedures, no matter how likely they are to receive an MDR reportable event (21 CFR 803.17)
- Manufacturers must maintain MDR files, which includes records of complaints and MDR reports, for a period of two years or the expected life of the device, if longer
- Manufacturers must report adverse events in foreign countries involving devices that are also marketed in the U.S. (49 Fed. Reg. 36,333)
- There are no special requirements for foreign manufacturers (21 CFR 803.58 has been stayed indefinitely)

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MDR Requirements for Device User Facilities

- Device user facilities are also required to report deaths and serious injuries to which a device has or may have caused or contributed
  - Reports of deaths are submitted to the manufacturer and the FDA
  - Reports of serious injuries are submitted to the manufacturer, unless the manufacturer is unknown (then the event is reported to the FDA)
- A device user facility is defined as a hospital, an ambulatory surgical facility, a nursing home, an outpatient treatment facility, or an outpatient diagnostic facility **which is not a physician's office**
- Device user facilities must establish and maintain adverse event files, and have a written MDR procedure
- FDA recently cited a number of LASIK ambulatory centers for failing to have written MDR procedures

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Reporting Corrections and Removals

- 21 C.F.R. Part 806 requires manufacturers to submit reports of corrections and removals to the FDA
  - Correction means the repair, modification, adjustment, relabeling, destruction, or inspection (including patient monitoring) of a device without its physical removal from its point of use
  - Removal means the physical removal of a device from its point of use for repair, modification, adjustment, relabeling, destruction or inspection
- Corrections and removals are reportable when done to:
  - Reduce a risk to health posed by the device
  - Remedy a violation of FDA's laws which may present a risk to health

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Exceptions to Reporting Corrections and Removals

- Actions to improve performance or quality but do not reduce a risk to health or remedy a violation
- Market withdrawals
  - Involve a minor violation that would not be subject to legal action by the FDA, or involves no violation
- Routine servicing
  - Regularly scheduled maintenance, including replacement of parts at the end of their normal life expectancy, not repairs of an unexpected nature
- Stock recovery
  - Devices that have not been marketed or left the direct control of the manufacturer

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Timeframes for Reporting

- MDR
  - Five (5) days from becoming aware of an MDR reportable event that necessitates remedial action
  - Thirty (30) days from becoming aware of any other MDR reportable event
  - Device user facilities have ten (10) days to report an MDR reportable event
- Corrections and removals
  - Ten (10) days from initiating the correction or removal

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Recalls

- A correction or removal is also a recall
- A recall, by definition, involves an actionable violation of FDA's laws
- The recall regulations at 21 C.F.R. Part 7, Subpart C do not include mandatory reporting requirements for manufacturers
- FDA's recall regulations describe classifying a recall and developing effective recall notifications

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Recall Classification

- The recall classification is derived from FDA's health hazard analysis
- Recalling firms should present their own health hazard analysis to ensure the most lenient classification is assigned
- The recall classification and health hazard analysis determine the level of recall effectiveness checks required and the extent of public notice

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Recall Classification

- Class I – reasonable probability that the use of, or exposure to, a violative product will cause serious adverse health consequences or death
- Class II – use of, or exposure to, a violative product may cause temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequences is remote
- Class III – use of, or exposure to, a violative product is not likely to cause adverse health consequences
- Class III recalls are generally considered to be not reportable under 21 C.F.R. Part 806 as a correction or removal

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Medical Device Tracking

- By order from the FDA, some manufacturers are required to track devices from their manufacture through the distribution chain
- The types of devices subject to a tracking order may include any Class II or Class III device:
  - the failure of which would be reasonably likely to have serious adverse health consequences;
  - which is intended to be implanted in the human body for more than one year; or
  - which is intended to be a life sustaining or life supporting device used outside a device user facility

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522 Postmarket Surveillance Studies

- Postmarket surveillance plans may use any approach that will produce a scientifically sound answer to FDA's question, including:
  - Randomized controlled clinical trials
  - Non-randomized controlled cohort studies
  - Detailed review of complaint history and scientific literature
  - Telephone or mail follow-up of a defined patient sample
  - Non-clinical testing of the device
  - Use of secondary data sets (e.g., Medicare), registries (e.g, Society for Interventional Radiology stent registry), internal registries, or tracking systems

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Medical Device Tracking

- Device tracking is intended to ensure that manufacturers will be able to promptly locate devices in commercial distribution, and to facilitate notifications and recalls ordered by FDA
- Manufacturers of a tracked device must establish a written standard operating procedure (SOP) which includes a method for tracking the device throughout distribution and a quality assurance program including audit procedures
- Final distributors of tracked devices are required to provide manufacturers with patient information

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522 Postmarket Surveillance Studies

- Section 522 of the Federal Food, Drug and Cosmetic Act gives FDA the authority to require a manufacturer to conduct postmarket surveillance of a class II or class III device that meets any of the following criteria:
  - its failure would be reasonably likely to have serious adverse health consequences;
  - it is expected to have significant use in pediatric populations;
  - it is intended to be implanted in the body for more than one year; or
  - it is intended to be a life-sustaining or life-supporting device used outside a device user facility
- FDA generally applies a “most practical, least burdensome” approach to reviewing a manufacturer’s proposed postmarket surveillance plan

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Medical Device Advertising and Labeling Requirements

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Authority of the FDA and the FTC

- The Food and Drug Administration ("FDA") regulates:
  - Labeling for all devices
  - Advertising for restricted devices only
- The Federal Trade Commission ("FTC") regulates advertising for non-restricted devices and for the provision of services using restricted devices
- Restricted devices are products that may be sold, distributed, or used only on a licensed practitioner's authorization or under conditions established by a PMA order or regulation

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“Labeling” Defined

- All labels and other written, printed, or graphic matter
  - upon any article or any of its containers or wrappers, or
  - accompanying such article at any time while an FDA-regulated product is held for sale after shipment or delivery for shipment in interstate commerce.
- “Accompanying" is interpreted liberally to mean more than physical association with the product. It extends to posters, tags, pamphlets, circulars, booklets, brochures, instruction books, direction sheets, fillers, websites, etc.

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“Advertising” Defined

- According to drug regulations, “[a]dvertisements . . . include advertisements in published journals, magazines, other periodicals, and newspapers, and advertisements broadcast through media such as radio, television, and telephone communication systems.” [21 C.F.R. 202.1(l)(2)]
- According to an appellate court decision: "Most, if not all advertising, is labeling. The term 'labeling' is defined in the FFDCA as including all printed matter accompanying any article. Congress did not, and we cannot, exclude from the definition printed matter which constitutes advertising."

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Labeling is a Broad Concept

- Labeling is anything written which:
  - Supplements or explains the product;
  - Is disseminated by the manufacturer; and
  - Reaches the customer, doctor, or patient before, with, or after the product

- Labeling includes:
  - Labels
  - Product inserts
  - Brochures
  - Promotional mailings
  - Posters
  - Correspondence with physicians
  - Scientific journal articles
  - E-mails
  - Websites

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FDA Labeling Requirements

- Labeling can encompass almost ANY printed information disseminated by a manufacturer
- Labeling may not be false or misleading in any particular [21 U.S.C. § 352(a)]
  - Affirmative misstatements about the device;
  - Failure to reveal material facts; or
  - Misrepresentations about another device [21 C.F.R. § 801.6]
- Labeling is limited to uses that have been cleared or approved by the FDA

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Other FDA Restrictions on Promotional Statements

- Any representation that creates an impression of official approval of a device because of complying with the premarket notification regulations is misleading and constitutes misbranding [21 C.F.R. § 807.97]
- Any representation that creates an impression of official approval because of registration or possession of a registration number is misleading and constitutes misbranding [21 C.F.R. § 807.39]
- A sponsor or investigator shall not:
  - Promote or test market an investigational device, until after FDA has approved the device for commercial distribution [21 C.F.R. § 812.7(a)]
  - Represent that an investigational device is safe or effective for the purposes for which it is being investigated [21 C.F.R. § 812.7(d)]

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Prohibited “Off-Label” Promotion

- Promotion of a use that has not been cleared or approved by the FDA,
- Promotion of **some** indications that are more specific than the cleared or approved indication
- Use of medical journal articles and medical or scientific reference publications in violation of FDA’s Good Reprint Practices Guidance

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"Practice of Medicine" Exception

- Physicians may use an approved or cleared device for any use, including off-label uses
- Physicians must be careful about promoting a device for off-label use
- A manufacturer may be responsible for off-label claims made by a physician or other third party, if:
  - A financial relationship between the physician and manufacturer exists;
  - Statements are made at the request of the manufacturer; or
  - Manufacturer uses physician's statements in labeling

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Good Reprint Practices

- Allows manufacturers to distribute scientific or medical journal articles that discuss the off-label use of a marketed device
- Among FDA's suggested requirements, articles must:
  - Be peer-reviewed, unabridged, and accompanied by labeling
  - Disclose potential conflicts of interest by authors
  - Not be highlighted or marked-up by the manufacturer, or distributed with promotional materials
  - Include a statement that the use has not been approved or cleared by FDA

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Good Reprint Practices (cont'd)

- The scientific or medical journal article should:
  - concern adequate and well-controlled clinical investigations that are considered scientifically sound by experts with scientific training and experience to evaluate the safety or effectiveness of the device;
  - not pose a significant risk to the public health, if relied upon; and
  - not be false or misleading, for example:
    - be characterized as definitive if a significant number of other studies contradict the conclusions;
    - have been withdrawn by the journal or disclaimed by the author; or
    - discuss a clinical investigation that FDA has stated is not adequate and well-controlled.

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Consequences of Illegal FDA Promotion

- Manufacturers and **individuals** are subject to FDA enforcement actions including:
  - Untitled or Warning letters
  - Injunction
  - Seizure
  - Civil penalties
  - Criminal prosecution
- FDA may require:
  - Corrective labeling
  - Dear Doctor letters
  - Filing a new premarket submission [510(k) or PMA]

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FTC Requirements

- Under the Federal Trade Commission Act:
  - Advertising must be truthful and non-deceptive;
  - Advertisers must have evidence to back up their claims; and
  - Advertisements cannot be unfair

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FTC Requirements (cont'd)

- Deceptive advertising:
  - Is likely to mislead consumers acting reasonably under the circumstances; and
  - Is material (important to a consumer's decision to buy or use the product)
- Unfair advertising:
  - Causes or is likely to cause substantial consumer injury which a consumer could not reasonably avoid; and
  - Is not outweighed by the benefit to consumers

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Types of Advertising Focused on by the FTC

- Ads that make claims about health or safety, such as:
  - “ABC Sunscreen will reduce the risk of skin cancer”
  - “ABC Water Filters remove harmful chemicals from tap water”
  - “ABC Chainsaw’s safety latch reduces the risk of injury”
- Ads that make claims that consumers would have trouble evaluating for themselves, such as:
  - “ABC Refrigerators will reduce your energy costs by 25%”
  - “ABC Gasoline decreases engine wear”
  - “ABC Hairspray is safe for the ozone”
- Ads that make subjective claims or claims that consumers can judge for themselves (for example, "ABC Cola tastes great") receive less attention from the FTC

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Penalties Imposed by the FTC

- Cease and desist orders
  - Legally-binding orders requiring companies to stop running deceptive ads, to have substantiation for claims in future ads, to report periodically to FTC staff about the substantiation they have for claims in new ads, and to pay a fine of $16,000 per day per ad if the company violates the law in the future.
- Civil penalties, consumer redress and other monetary remedies
  - Civil penalties range from thousands to millions of dollars, depending on the nature of the violation, as well as full or partial refunds to all consumers who bought the product.

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Penalties Imposed by the FTC (cont'd)

- Corrective advertising, disclosures and other informational remedies
  - Advertisers have been required to take out new ads to correct the misinformation conveyed in the original ad, notify purchasers about deceptive claims in ads, include specific disclosures in future ads, or provide other information to consumers.

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Remedies Available to Competitors

- Federal and state statutes that protect businesses from unfair competition. For example, the Lanham Act gives companies the right to sue their competitors for making deceptive claims in ads.
- File complaint with the National Advertising Division (NAD) of the Council of Better Business Bureaus (a private, self-regulatory group).
- Contact the FDA or the FTC.
- FDA allegations that device labeling or advertising contains false or misleading information may be used as evidence in product liability suits.

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False Claims Act

- FDA violations, including those related to advertising and labeling, can form the basis of a False Claims Act charge [31 U.S.C. §§ 3729 – 3733]
- The False Claims Act imposes liability on any person or entity who, among other actions:
  - Knowingly presents, or causes to be presented a false claim for payment or approval;
  - Knowingly makes, uses, or causes to be made or used, a false record or statement material to a false or fraudulent claim; and
  - Conspires to commit any violation of the False Claims Act.

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False Claims Act (cont'd)

- False or misleading advertising or labeling can cause a false claim to be presented for payment or approval
- How? Use of the product (induced by the false or misleading advertising) was paid through a federal or state healthcare program or hospital:
  - Medicare
  - Medicaid
  - Government run hospitals (VA, military), or
  - Any other state or government run system that pays for healthcare

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False Claims Act Penalties

- Repayment
- Treble damages
- Civil Monetary Penalties
- Exclusion from participation in Medicare, Medicaid, or any other state or federal healthcare program
  - Doctors would be unable to obtain funds from state or federal healthcare programs for the use of the device

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Seth Mailhot is a partner and lead of the FDA Regulatory Practice Group in Michael Best & Friedrich's Washington D.C. office. His 14 years working in the U.S. Food and Drug Administration (FDA) has provided him a unique perspective when counseling clients on a broad range of matters involving the FDA.

Seth's practice includes representation of the medical device, pharmaceutical, dietary supplement, tobacco and food industries, and covers both premarket and post-market issues. His practice is focused on development of premarket submission strategies, and FDA enforcement of good manufacturing practices, both domestically and abroad.

Admissions

- District of Columbia
- Massachusetts
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Education

- New England School of Law, J.D., Valedictorian, *summa cum laude*
- University of Massachusetts, B.S., Chemical Engineering