

# How to Complete a 510(k) Submission

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# Key Objectives

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- I. Background on U.S. Medical Device Law
- II. Understanding the legal framework for 510(k) determinations
- III. 510(k) drafting: Beyond the basics
  - A. Predicates: researching predicates, combination predicates, and preamendments predicates
  - B. Strategy: choosing the right claim and introducing new features
  - C. Assessing data requirements/presubmission meetings
- IV. What to do when your substantial equivalence argument is rejected
- V. Special topics: software, combination products
- VI. Device modifications - Choosing the right regulatory mechanism
- VII. Lessons learned: seeing the 510(k) from the reviewer's perspective
- VIII. Postmarket Requirements

# Background on U.S. Medical Device Regulation



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# FDA's Definition of Medical Device

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- Intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease
- Intended to affect the structure or any function of the body
- Does not achieve its primary intended purposes through chemical action
- Is not dependent upon being metabolized to achieve any of its primary intended purposes

# Classification of Devices: Class I

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- Devices for which general controls are sufficient to provide reasonable assurance of safety and effectiveness
- Examples: scalpels; tongue depressors

# Classification of Devices: General Controls

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- Adulteration and misbranding provisions
- Registration and listing
- Premarket notification (510(k)) (for a *limited* number of Class I devices)
- Notification and repair
- Replacement or refund
- Records and reports
- Banned devices and
- Good Manufacturing Practices (unless exempt)

# Classification of Devices: Class II

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- Devices for which general controls alone are insufficient to establish safety and effectiveness. Class II devices must meet general controls (including premarket notification requirements *unless exempt*) as well as Special Controls, if applicable.
- Examples: Many IVDs, lithotripters, lasers for general surgery, diagnostic ultrasound

# Classification of Devices: Special Controls

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- Special Controls
  - Performance standards
  - Postmarket surveillance
  - Patient registries, guidelines recommendations, and “other appropriate actions”

# Classification of Devices: Class III

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- Devices for which general and special controls alone are not sufficient to establish safety and efficacy and devices that:
  - (i) are used in supporting or sustaining human life or
  - (ii) are for a use which is of substantial importance in preventing impairment of human health or
  - (iii) present a potential unreasonable risk of illness or injury.

# Classification of Devices: Class III

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- Most class III devices require approval of a Premarket Approval Application unless PMAs have not been called for
  - FDA has recently called for PMAs for most of the remaining “Pre-Amendments” devices
- Examples: Many spinal implants, artificial hearts, lasers for ophthalmic surgery

# How Do You Know Which Class You Are In?

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- Code of Federal Regulations
- Predicate Device Search
- Informal or Formal Inquiry to FDA
- Submit a 510(k)

***Claim-dependent***

# Determine What “Bucket” You Are In

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To market a device in the U.S., a medical device manufacturer must follow one of the following routes:

- 510(k) Premarket Notification
- De Novo Review
- PMA Process
- PDP Process

# 510(k) Notices are Required For:

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- Small number of Class I devices (specifically called out in the regulations)
- Most Class II devices
- Preamendment Class III devices (marketed post-1976) for which PMAs are not currently required
  - FDA has recently called for PMAs for 25 of 27 of the remaining class III Pre-Amendments devices

# PMAs are Required For

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- Most Class III devices
- Could be Class III because of high risk or because of lack of predicate device
- Intended use, indications for use, or technological characteristics could move an otherwise Class II device into Class III
- Once a device is in Class III for a certain indication, all devices of that kind must have a PMA (unless the device is downclassified)

# How Do PMAs and 510(k)s Differ?

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- Volume of Information
- Clinical Study Requirements (follow-up and analysis)
- Bioresearch Monitoring Inspections
- Extensive Labeling Review
- Manufacturing Information
- Panel Review
- Time to Approval

# PMA vs. 510(k)

- **PMA**

- Safety and Effectiveness
- Scientific Evidence
- Almost Always Accompanied by Clinical Data – controlled randomized study
- Detailed, Lengthy Application
- Must be “Approved” Prior to Marketing
- Pending PMA is Confidential; Following Approval, Summary Information is Released
- 180 Day Review Cycle; average FDA review time: 284 days (06 FY)
- Conditions of Approval
  - Annual Report; post-approval study; PMA Supplement for changes; and adverse reaction and device defect reporting
- FY 2007, 27 PMAs approved

- **510(k)**

- Substantial Equivalence
- Comparison to Existing (Predicate) Device
- Possibly Contains Clinical Data (10 - 15% of 510(k)s)
- Shorter
- Must be “Cleared” Prior to Marketing
- Pending 510(k) is Confidential; Following SE Determination Entire 510(k), Less Company Proprietary Data, is Released; 510(k) Summary Available 30 Days After Clearance
- 90 Day Review Period for Traditional 510(k) notices; 30 Day Review Period for Special 510(k) notices; average FDA review time: 54 days (06 FY)
- New 510(k) for significant changes
- FY 2007, 3502 510(k)s cleared

# Understanding the Legal Framework – 510(k)s



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# Section 510(k) of the Act

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- Requires companies to “notify” FDA 90 days before they propose to begin marketing a new device or certain modified devices
- However, in reality, a 510(k) is much more than a “notice,” and marketing cannot begin until clearance
- Purpose is to permit FDA to determine whether the device is truly novel and requires proof of safety and efficacy or whether it is similar enough (“substantially equivalent”) to a device already on the market (a “predicate”) to permit marketing without as detailed a review as a PMA
- FDA has considerable discretion to decide whether a product requires a 510(k) or a PMA

# General Criteria to be Deemed Substantially Equivalent Device:

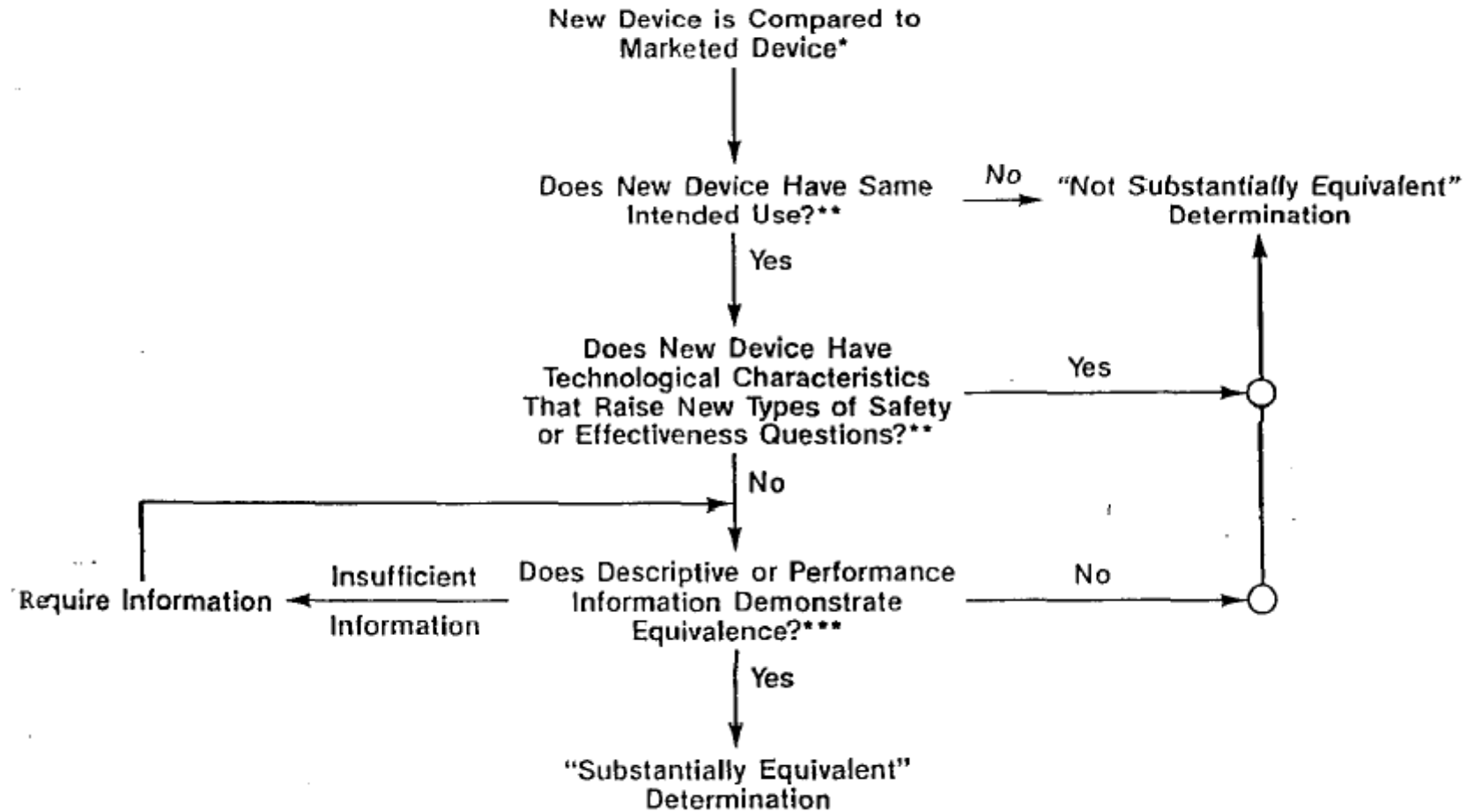
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## Two key criteria for new device to be SE:

1. Same intended use and similar indications for use; and
2. Same or similar technological characteristics.

***Substantial equivalence must be based on comparison to a legally marketed predicate***

# 510(k) Decision Making Process



# Criteria for SE Finding from Mohan Memorandum (#K86-3)

- The new device has the same intended use; **and**,
- The new device has the same technological characteristics, (i.e., same materials, design, energy source, etc.); or, it has new technological characteristics that could not affect safety or effectiveness; **or**
- It has new technological characteristics that could affect safety or effectiveness, **and**
- There are accepted scientific methods for evaluating whether safety or effectiveness has been adversely affected as a result of the use of new technological characteristics; **and**
- There are data to demonstrate that the new technological features have not diminished safety or effectiveness.

# Predicates



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# What Can Be Used as a Predicate?

- Legally marketed class I or II device, whether exempt or 510(k) cleared
- Class III device for which FDA has not yet called for PMA applications
- Preamendments devices, with proper documentation of commercial use before 1976
- Predicate that was cleared via *de novo* route
- NOT class III devices with PMA approval, no matter how many have been approved, unless downclassified

# Combination Predicates

- Combinations of predicates can be used
  - Established in 1986 guidance (“Mohan Memorandum”)
  - May use multiple predicates to demonstrate similarity of new device to prior technology
    - *Example:* same dimensions as one predicate, same materials as another
    - More challenging: same indications as one predicate, same technology as another
  - If no predicate with both same indications and similar technology, more supporting data may be needed
  - *Example:* RF ablation device for fecal incontinence
    - Potential predicates may include RF devices for shrinking other soft tissues and biofeedback devices for incontinence
- Increasing resistance to combination predicate arguments

# How to Identify and Research Predicates

- If you know your competition, you probably know your predicates
- If novel technology, understanding the medical area of interest is key
- Start with broad review of medical literature to understand how the device fits into the continuum of care
- Patent searches can also be helpful as a starting point if no obvious choices
- Search strategies
  - Search key terms in product classification database, then enter relevant product codes in 510(k) database
  - Enter key terms in “device name” field in 510(k) database available at: <http://www.fda.gov/cdrh/510khome.html#database>
  - Use “panel” field in 510(k) search engine to narrow choices
- Sometimes there is no clear predicate, e.g., where device replaces or automates a surgical technique or a clinical judgment

# Strategy Considerations: Choosing the Right Claim and Introducing New Features



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# General Criteria to be Deemed Substantially Equivalent

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- Intended Use
  - Describes general purpose for which the device is used
  - Must be exactly the same as predicate
  
- Indications for use
  - Higher degree of specificity than intended use
  - May describe a specific diagnostic or therapeutic purpose
  - May include a description of the population, the environment of use
  - Prescription versus OTC
  - Indications need not be identical but differences should not alter the intended diagnostic or therapeutic effect, considering the effect on safety and effectiveness

# Comparison of Intended Use/Indications

- *Example:* RF ablation for palliative treatment of inoperable liver cancer
  - Intended use: Soft tissue ablation
  - Indications for use: palliative treatment of inoperable liver cancer
- In drafting 510(k) substantial equivalence argument, first step is to identify predicates and draft an intended use statement that is common to new device and predicate
- If there are differences in indications, must next demonstrate why those differences do not alter intended diagnostic or therapeutic effect, considering impact on safety and effectiveness
- Off-label use of predicate cannot be used to support an SE finding no matter prevalent

# Choice of Intended Use/Indications for Use

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- Can have a big impact on relative difficulty/ease of 510(k) clearance
  - *Example:* Tool versus treatment
- Generally best to “start small,” work incrementally
- In some cases, there is a “bright line” that divides claims that can be cleared in a 510(k) from those that require a PMA
  - *Example:* diagnosis versus screening
    - Time difference of years to clearance/approval

# Choice of Indications and Off-Label Use

- Clearing device for more general use first to permit more straightforward pathway/less onerous data requirements is generally desirable, BUT
  - If extensive off-label use is expected, or if the off-label use is really the only use, this can be problematic
  - Potential for FDA enforcement action
  - “Black box” warning language in labeling per 513(i)(1)(E)
  - Products liability
    - Cannot provide adequate directions/warnings for the off-label use without making the product adulterated and/or misbranded
  - May also be reimbursement issues if device indication does not match its principal use
  - Examples – Cardiac catheters used for ablation; biliary stents used in the peripheral vasculature

## Section 513(i)(1)(E)

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- Section 513(i)(1)(E) of the Federal Food, Drug, and Cosmetic Act generally limits the determination of the intended use of a device that is the subject of a premarket notification (510(k)) to the proposed labeling contained in the submission
- Off-label uses may not be considered unless
  - There is a “reasonable likelihood” that the device will be used for an intended use other than that in the proposed labeling; **and**
  - That use could cause harm
- If FDA finds there is likely off-label use that could cause harm, must notify applicant:
  - Sponsor can modify the device design to address the off-label use; or
  - Sponsor can request a written determination from the FDA Office Director;
  - FDA can issue a SE letter with limitations specifying appropriate limitation regarding the off-label use to be included in the labeling for the device.

# General/Specific Use Guidance

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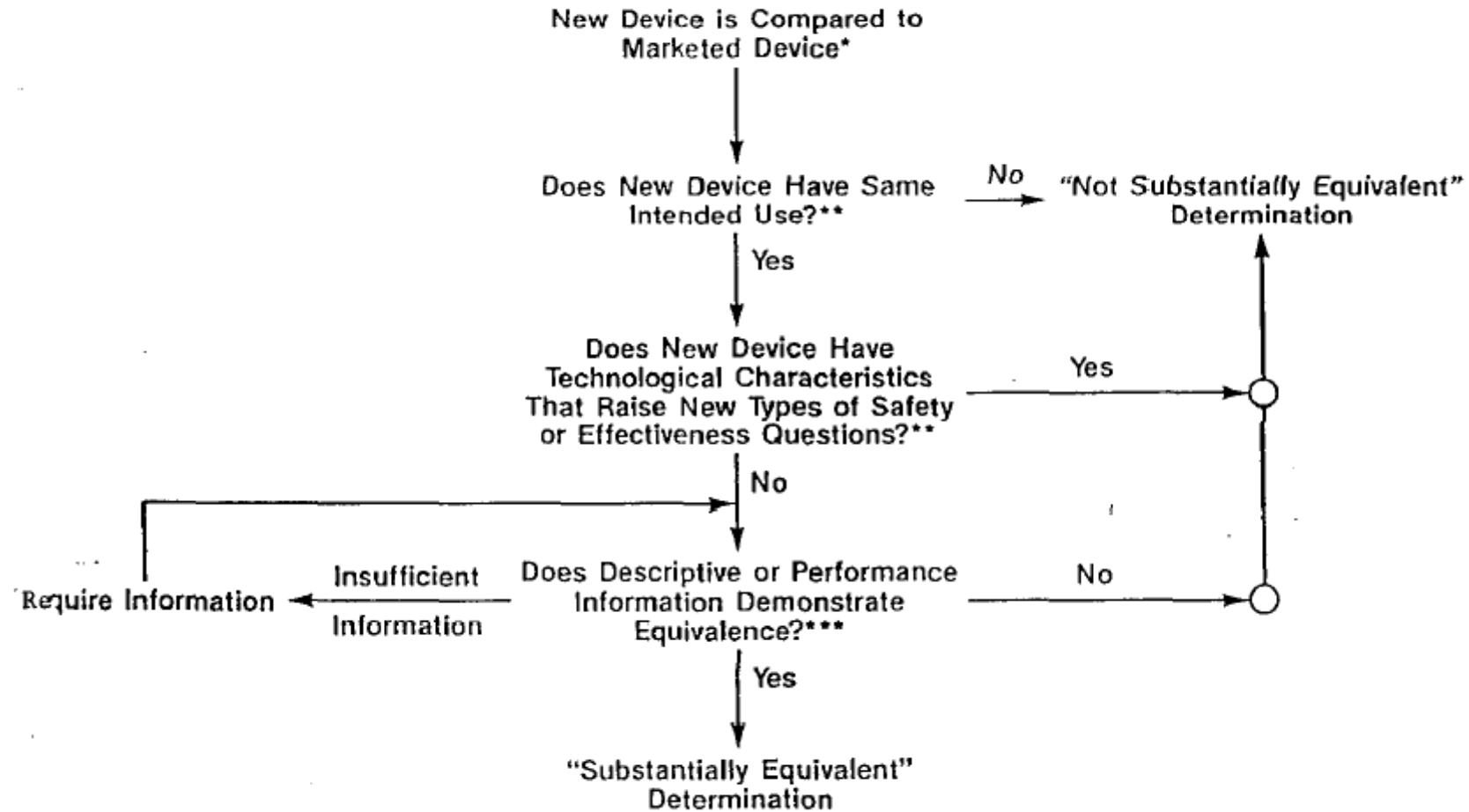
- When does general not encompass specific?
- FDA guidance provides guiding principles that FDA considers when a more specific indication for use may be reasonably included in the general indication for use
- Show substantial equivalence to device with general indication
- Submit 510(k) rather than PMA
- Decision factors:
  - Risk
  - Public Health Impact
  - Knowledge Base
  - Endpoints
  - Tool or Treatment
  - Design Changes

# Examples

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- Diagnostic Ultrasound
  - General Indication: Evaluation of soft tissue
  - Specific Indication: Aid in differentiating benign from malignant breast lesions
  - Determination: **NSE** because:
    - Risk of false negatives higher in breast
    - Measurement of breast cancer has major public health impact
    - Major change in using ultrasound to recommend breast biopsy or not
- Diagnostic Ultrasound
  - General Indication: Evaluation of soft tissue
  - Specific Indication: discrimination of small soft tissue parts (e.g., tendons, nerves)
  - Determination: **SE** because
    - No significant risk
    - Simply a statement of the types of anatomical detail

# 510(k) Decision Making Process



# Comparison of Technological Characteristics

- A device is SE to another device if it has the same intended use and either (i) the same technological characteristics or
- (ii) different technological characteristics but is as safe and effective as the other device and does not raise different questions of safety or effectiveness. FDCA § 513(l)(1)(A)g, 21 U.S.C. § 360c(l)(1)(a)
- New or different technological characteristics include modifications in:
  - Design;
  - Materials;
  - Energy source; or
  - Principle of operation

# Comparing Technological Characteristics

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- Making persuasive arguments:
  - Remember that new/different technological features can impact safety and effectiveness without being NSE
  - Important not to avoid obvious differences—instead, explain why the differences do not raise new types of safety or effectiveness issues
  - *Example:* RF ablation of soft tissue versus high intensity focused ultrasound
    - Difference in technology could, in theory, impact safety or effectiveness
    - However, no new question of safety or effectiveness because heat is heat
    - Question of whether temperature is properly controlled/adequate heating for target ablation without extended area of thermal damage is common to both devices
    - Therefore, can be found SE
    - However, note that if HIFU is performed “closed” and RF “open,” this difference may raise new questions that has been found NSE due to inability to directly monitor temperature/extent of thermal effect

# Comparing Technological Characteristics

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- Making persuasive arguments:
  - Differences that are susceptible to standard bench testing to demonstrate they do not adversely impact safety or effectiveness generally SE
  - Differences that require clinical testing may also be SE but more challenging
  - Can be useful to compare to other predicates that arguably have more important but different technological differences and show they were found SE
    - *Example:* change in surgical technique for previously cleared orthopedic implant to use a new approach not used in any predicate
    - No predicate for approach, but first predicate for percutaneous approach found SE to predicates that were all implanted in open surgery
    - Argue change in approach is less significant than change from open to percutaneous

# How Much is Too Much?

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- If new claim with no strong predicate, may not want to change too many technological features in first submission
- Consider phased approach in which new indication is pursued first, followed by Special 510(k)s or other filings as appropriate for changes in technological features, OR
- Clear all new technological features first, then pursue new indication.

# Assessing Data Requirements



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# Determining What Data to Provide

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- Look for guidance documents
- Research 510(k) summaries for predicates
- Buy redacted copy of one or more predicate 510(k)s
- Research industry standards
- Search medical literature to see what testing of predicates has been reported
- Generally, the amount and type of data increases with the degree of novelty/complexity of the device
- Although only 5-10% of 510(k)s include clinical data, the most novel products may be more likely to require clinicals
- *Example:* Predicate 510(k) used cadaver testing only to support change from open to percutaneous surgical technique; description of method for cadaver test redacted from 510(k) but available in published medical literature.

# When is a Presubmission Meeting Warranted?

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- When a clinical study may be necessary
- When an expensive or lengthy preclinical test may be necessary
- When there is no guidance/little precedent/no industry standards
- When 510(k) pathway is unclear/de novo may be a possibility
  - Typically takes up to 60 days to schedule meeting after background package is submitted
  - However, up front time may save subsequent review time

# Putting it All Together



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# Information Required in a 510(k) 21 CFR § 807.87

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- I. Name of Device
  - Classification Name
  - Common Name
  - Proprietary Name
- II. Establishment Registration Number and Address
- III. Classification of Device/Classification Panel
- IV. Performance Standards
- V. Labeling

# Information Required in a 510(k) (cont'd)

- VI. Device Description/Substantial Equivalence
- VII. Software
- VIII. Performance Testing - Examples:
  - Thermal, Mechanical, and Electrical Safety
  - Electromagnetic Compatibility/Electromagnetic Interference
  - Biocompatibility
  - Sterilization/Cleaning/Disinfection
- IX. Animal and Clinical Data (if applicable)
- X. 510(k) Summary

# Information Required in a 510(k) (cont'd)

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- XI. Confidentiality
- XII. Submitter's Name and Address
- XIII. Contact Person and Telephone/Fax Nos.
- XIV. Indications for Use Statement
- XV. Truthful and Accurate Statement
- XVI. Financial Disclosure

# FDA's August 2005, 510(k) Format Guidance

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- Changed the order of information presented in the 510(k) submission
- Added an Executive Summary section (summary of device description, SE comparison table, and performance testing)
- Specifies Content of the cover letter for the submission

# Examples of Attachments for a 510(k) Notice

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- Proposed Labeling And Operating Manual
- Drawings And Photographs
- Substantial Equivalence Chart
- Labeling For Predicate Devices
- Software Information
- Performance Testing
- Biocompatibility Testing/Certification
- Sterility Testing
- Pyrogen Testing
- 510(k) Summary or Statement
- Truthful And Accurate Statement
- Indications For Use Statement
- User Fee Cover Sheet

# Confidentiality of Information in a 510(k)

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- Currently FDA does not disclose existence of a 510(k) that is under review
- Existence of 510(k) is disclosable as soon as SE/NSE determination is made - No extended confidentiality
- Trade secret and confidential commercial information is protected
- FDA must notify submitter before releasing contents of 510(k); applicant has opportunity to redact
- 510(k) summary or statement must be made available and is posted on FDA web site

# Device Modifications



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# Device Modifications

- A new 510(k) notice must be filed for a legally marketed device if it is about to be significantly modified in design, components, method of manufacture, or intended use.
- Significant modifications include:
  - Changes that could significantly affect safety or effectiveness, e.g., a significant change in design, material, chemical composition, energy source, or manufacturing process.
  - Major changes in the intended use of the device.

# Determining Whether a 510(k) Must Be Submitted for a Device Modification

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- Is the proposed modification “significant”?
- Does it effect a major change in the intended use?
- “Could” it significantly affect safety or effectiveness?
- Company makes first decision, but FDA can disagree.

# FDA's 510(k) Modification Guidance

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- Manufacturers and FDA often had difficulty interpreting what types of modifications were “significant”; what types of changes to the intended use were “major”; and when a change “could significantly affect safety or effectiveness.”
- The guidance clarifies the meaning of terms such as “major” and “significant.”
- The guidance provides separate analyses for the following types of changes:
  - Labeling changes
  - Technology, engineering, and performance changes; and
  - Materials changes (IVDs and non-IVDs)
- If conclusion is made that no new 510(k) is required, documentation in memo to file showing the logic on proper flow chart, together with appropriate supporting data, is important
  - “Quality” memo to file may be similar amount of work to a Special 510(k), but do not need to await clearance
  - Even if FDA disagrees with a decision not to file in an inspection, a thorough memo to file may help to reduce risk of enforcement
- Cumulative effect of multiple changes should be considered

# Technology, Engineering, and Performance Changes

- All changes in technology, engineering, and performance are evaluated and validated according to QSR requirements to determine if a new 510(k) notice must be filed.
- Examples of technology, engineering, and performance changes that generally require a new 510(k) notice:
  - Changing the control mechanism (*i.e.*, analog to digital control; pneumatic to electronic control, etc.)
  - Changing the operating principle;
  - Changing the energy source; or
  - Changing the sterilization procedure in a manner that affects performance specifications or reduces the sterility assurance level.
- Other types of engineering changes, *i.e.*, changes to the performance specifications, the dimensional specifications, and the software/firmware, may not require a new 510(k) if:
  - They do not affect the indications for use;
  - They do not require supporting clinical data on safety and effectiveness for purposes of determining substantial equivalence; and
  - The results of design validation do not raise new issues of safety and effectiveness.

# Choosing the Right Mechanism



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# New 510(k) Paradigm for Alternate Approaches to Market Clearance

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- FDA has developed “The New 510(k) Paradigm” (March 20, 1998) which offers manufacturers two new optional approaches for obtaining clearance
  - (1) the “Special 510(k): Device Modification”
  - (2) the “Abbreviated 510(k)”

# Special 510(k): Device Modification

- If a new 510(k) is required for a device modification and if the change does not:
  - (1) affect the intended use of the device; or
  - (2) alter the fundamental scientific technology of the device
- A Special 510(k) may be submitted
- FDA generally processes Special 510(k)s within 30 days
- Not usually appropriate if clinical data is needed to support the change

# Special 510(k): Device Modification

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- The company must conduct a risk analysis and the necessary verification and validation activities to demonstrate that the design outputs of the modified device meet the design input requirements
- The basic content requirements of a 510(k) remain the same but the intent is that less data will be required in the 510(k) than in the past to support the change
- The submission must include a concise summary of the company's design control activities and a Declaration of Conformity with the design control requirements

# Abbreviated 510(k)s

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- Device manufacturers may submit an Abbreviated 510(k) when:
  - (1) a device-specific guidance document exists;
  - (2) a special control has been established; or
  - (3) FDA has recognized a relevant consensus standard
- 510(k) must include the required elements of a premarket notification

# Abbreviated 510(k)s

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- An Abbreviated 510(k) that relies on a guidance document and/or special control(s) should include a summary report that describes how the guidance document and/or special control(s) were used during device development and testing
- Abbreviated 510(k)s that rely on a recognized standard should include a declaration of conformity to the standard instead of the summary report

# Recognition and Use of Consensus Standards

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- Information on conformance with recognized consensus standards may help establish the substantial equivalence of a new device to a legally marketed predicate
- This information can be used to show that the new device is as safe and effective as the predicate in the areas covered by the consensus standard(s)
- A premarket submission containing a declaration of conformity to the recognized consensus standards, in most cases, will eliminate the need to review the actual test data for those aspects of the device addressed by the standards
- Conformance is voluntary

# What to Do if Your Device is Found NSE?



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# The Sky is Not Falling . . .

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- If an NSE decision is reached, the manufacturer may not go to market. Options then include:
  - Informal “Appeal”
  - Resubmit another 510(k) with new information or data
  - “De Novo Process”
  - File reclassification petition
  - Submit a PMA
- Exploring reasons for NSE decision are the key to deciding which course of action to take
- Informal consultation with FDA, possibly followed by a meeting if necessary

# De Novo Review -- Evaluation of Automatic Class III Designation

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- Since 1997, FDA permits manufacturers of certain novel, low risk devices to request that the agency reconsider automatic class III determinations (*i.e.*, a determination that a medical device is a class III device because it lacks a legally marketed predicate device).
- This procedure is intended for novel but low risk devices.
- “De novo classification” procedure can be invoked after an NSE decision to request that FDA place the device in class I or II despite the absence of a predicate device, based upon reasonable assurance that the device is safe and effective

# De Novo Request

- Required elements:
  - A description of the device
  - Any available data from human experience with the device
  - Risks and benefits of the device
  - General and special controls the submitter believes applicable to the device
  - Submitter's recommendation for placement into Class I or Class II
  - Reasons for the classification the submitter recommends
- If FDA grants the request, the device is permitted to enter commercial distribution in the same manner as if 510(k) clearance had been granted.
- Can be used as a predicate in future submissions

# Special Topics



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# 510(k) User Fees

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- FY 2009 User Fees (Oct. 1, 2009 – Sept. 30, 2010)
  - Standard Fee - \$3,693
  - Small Business Fee - \$1,847
    - Firms with annual gross sales or receipts of \$100 million or less, including the gross sales and receipts of all affiliates, partners, and parent firms.
    - Newly enacted U.S. law now provides a way for foreign firms that do not file tax returns with the U.S. Internal Revenue Service to qualify for small business rates.

## FDA Performance Goals – 510(k)s

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- FDA has improved its performance goal framework to emphasize the agency’s deadlines for “final decisions,” and encourage a more informal, interactive process between the agency and industry.
- This emphasis on final decisions is in contrast to the agency’s previous premarket “cycle goals” scheme, which, for example, involved issuing deficiency letters within a specified time period.
- In contrast, the new goal framework emphasizes the time to final decision and encourages FDA reviewers to simply call or email a company when questions arise during the review process.
- For 510(k)s, these quantitative performance goals are as follows:

**90% of 510(k)s in 90 days**

**98% of 510(k)s in 150 days**

# Software

- Software encompasses:
  - Software in medical devices
    - Handles sample movement, equipment control
    - Also for raw data storage and retrieval, data acquisition, and software to process detected signals
    - May include analytical software used to calculate a clinical result
      - Compare specimen output to standard curve
      - Compare to table of “normal” values
  - Software as a stand-alone medical device
    - Stand-alone software applications
    - Marketed for a medical use or as an accessory to a medical device for a medical use

# Software Regulation

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- When a component of a medical device, software is regulated with the medical device
- When stand alone, software is regulated as a medical device, with limited exceptions (library or reference software)
- Either pathway requires:
  - A “Level of Concern” determination (Major, Moderate, or Minor)
    - Current trend is that most Minor levels of concern are being bumped to Major
  - OIVD considers most IVD software to be at a moderate level of concern
  - Based on risks due to software prior to mitigation
    - “Prior to mitigation of hazards, could a failure of the Software Device result in death or serious injury, either to a patient or to a user of the device?”

# Software Regulation

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- Documentation should be consistent with:
  - The intended use of the software device
  - The Level of Concern
  - The type of submission
- In general, software documentation in a submission should:
  - Describe the device/software design
  - Document how the design was implemented
  - Demonstrate how the software produced by the design implementation was tested
  - Show that hazards were appropriately identified and that risks were managed effectively
  - Provide traceability to link design, implementation, testing and risk management

# Stand Alone Software

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- “Competent human intervention”—does it still exist?
- Increase in FDA Untitled and Warning Letters

# Combination Products - Premarket

- Jurisdiction is determined by identification of the “Primary Mode of Action”
  - “Mode of action” - means by which product achieves therapeutic effect (21 CFR 3.2(k))
  - “Primary mode of action” – single most important mode of action to achieve therapeutic effect (greatest overall contribution) (21 CFR 3.2(m))
- Algorithm for Center assignment:
  - Identify modes of action
  - Assign jurisdiction to center responsible for most important mode of action
  - If indeterminate, assign to center that regulates combinations raising similar questions of safety and effectiveness
  - If indeterminate, assign to center with most expertise related to most significant safety and effectiveness questions

(21 CFR 3.4(b))
- Current Director of OCP is Thanh Nguyen
  - Empirically, we are seeing that many requests for designations are being assigned to the Center for Drug Evaluation and Research

# Combination Products

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- Examples of 510(k) cleared combinations:
  - Antibiotic bone cement
- Well characterized drugs less likely to trigger significant issues
- However, application of even a well known drug with a long history of safe use in a different application or via a different route can trigger questions
- Timing extended due to involvement of various staff with other commitments, need to coordinate feedback
- RFD sometimes required if lead center unclear when 510(k) submitted—  
check precedents before filing

# Lessons Learned: Seeing the 510(k) from the Reviewer's Perspective



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# Lessons Learned

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- Every reviewer cannot be an expert on every topic
  - Assuming too much knowledge causes delay, BUT
  - Don't reinvent the wheel
- Creative predicate arguments can make a difference
  - Don't expect FDA to do the predicate research for you or advise if better predicates are available, BUT
  - If FDA makes a suggestion about a predicate to use or to avoid, take it
  - FDA will sometimes express discomfort with previously cleared predicates, e.g., due to off-label use
- Don't gloss over key differences in technology—you are leaving the reviewer the hard work

# Lessons Learned

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- A 510(k) is not an epic novel . . . BUT
  - Including detail on issues the reviewer is very likely to raise may eliminate a round of review
  - Focus on key areas of technological difference
  - Not all technological features need to be discussed if there is no issue
  - Walking the reviewer through the entire 510(k) flow chart is important, since the reviewer will need to complete this exercise to reach a decision

# Lessons Learned

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- Choose the wording of the intended use and indications for use carefully
- Avoid implied claims of superiority/clinical performance unless there is strong supporting data ⇒ Stray statements in 510(k) or labeling can contradict the substantial equivalence argument
- Check the company's web site for similar claims before filing
- *Example:* 510(k) says nothing new, web site says “a revolutionary advance in the treatment of XX”

# Lessons Learned

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- Look critically at the predicate indications
  - 513(i)(1)(E) restrictions on predicates mean your device will have same restrictions
  - Concerns about off-label use can cause delay
  - If the wording of the predicate indications looks unusually specific or unusually general, may suggest that the claim had to be carefully negotiated with FDA
  - *Example:* Rejuvenique—“for cosmetic use”

# Lessons Learned

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- Critically review all performance test reports
  - Common pitfalls
    - Insufficient sample size (n=5 usually minimum FDA wants to see, sometimes much more)
    - Device changed since test performed, or finished, sterile product not used
    - No/inadequate justification for device size/model testing
    - No/inadequate rationale for test conditions
    - No/inadequate clinical rationale for acceptance criteria
    - No/inadequate justification for deviation from applicable standards
    - Direct comparison to predicate not performed
    - Outliers excluded without justification
    - Report contains extraneous information such as “design could be improved by doing XX, but costs too much.”

# Lessons Learned

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- Respond to all requests for additional information as quickly as possible, bearing in mind reviewer's deadlines, or communicate expected timeline for response
- Compare product labeling to predicates and be prepared to explain differences in warnings, precautions, contraindications
- ***Provide an electronic copy!***

# Lessons Learned

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- 510(k) Summary or Statement
  - Summary often better
  - Lengthens time to release of full 510(k)
  - Be strategic in content/detail; FDA will require substance, but no need to give away all details of test methodology
- Check off the “RX” or “OTC” box on the indications for use form

***Organization of the 510(k) is very important:***

***sloppy = delay***

# Recent Trends

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- MDUFMA user fees have tightened timeframes
  - Reviews generally cannot go on as long
  - Higher likelihood of NSE or request to withdraw if issues cannot be resolved in one or two cycles
  - More interactive and informal discussions
  - No review starts until user fee is paid
- Greater scrutiny of instruments/accessories
- Completion of sterilization validation more likely to be required, for products supplied sterile

# Recent Trends

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- Increasing resistance to combination predicate arguments
  - Resistance to both combinations of indications for use and technological aspects from different devices and combinations of technological characteristics from different devices
  - No uniform policy and seems to be branch specific
  - Higher levels of data required to address differences between new device and predicates
  - Bumping companies into PMA realm or *de novo* down classification
- Software level of concern (LOC)
  - Minor LOC often reclassified to moderate

# Recent Trends

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- Increasing data requirements overall and also to address differences between new device and identified predicate devices
  - Bench Data
    - FDA requesting additional data not required for predicates, including clinical data, even when predicate is an earlier version of the same device
  - Animal Studies
    - FDA has a number of specific people dedicated to the review of animal studies
    - More emphasis on conducting studies under Good Laboratory Practices (GLP)
  - Clinical data
    - Number of 510(k) notices requiring clinical data to support clearance has increased
    - Increasing level of data required for clinical studies
    - FDA requiring postmarket studies in certain cases

# Postmarket Regulation



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# Key Areas of Postmarket Regulation

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- Establishment Registration and Device Listing
- Quality System Requirements (“QSR”)
- Medical Device Reporting (“MDRs”)
- Corrections and Removals (Recalls)
- Imports and Exports

# FDA Enforcement Remedies

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- Inspectional Observations (FDA-483s)
- Warning Letters and Untitled Letters
- Product Seizures
- Administrative Detention
- Recalls (Voluntary and Mandatory)
- Application Integrity Program
- Injunctions
- Refusing Requests for 510(k) Clearance or Premarket Approval (“PMA”) of New Products as well as PMA Supplements
- Civil Monetary Penalties
- Criminal Fines and Penalties
- Import Alerts

# Import Alerts/Detentions

- FDA's ability to enforce its regulations (e.g., GMPs) is enhanced when products are being made outside of the United States
- Under broad grant of authority, the FDA can bar the entry of a product into the United States based on the mere appearance of adulteration or misbranding
- The FDA does not need a court order to initiate such action — the action can be initiated by the FDA and U.S. Customs and Border Protection Agents at the port of entry
- FDA also can issue an Import Alert, also known as a 'detention without physical examination' to bar admission of a particular product. Import Alerts also can be product-specific, or apply to every product that is manufactured at a particular foreign facility

## Questions?

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- CDRH Web Site: [www.fda.gov/cdrh](http://www.fda.gov/cdrh)
- Device Advice
- Topic Index—Premarket Notification
  
- Contact: [mshey1@hhlaw.com](mailto:mshey1@hhlaw.com) (202) 637-5456