Improving Your Chances for Success: Understanding 510(k) Guidance and Procedures

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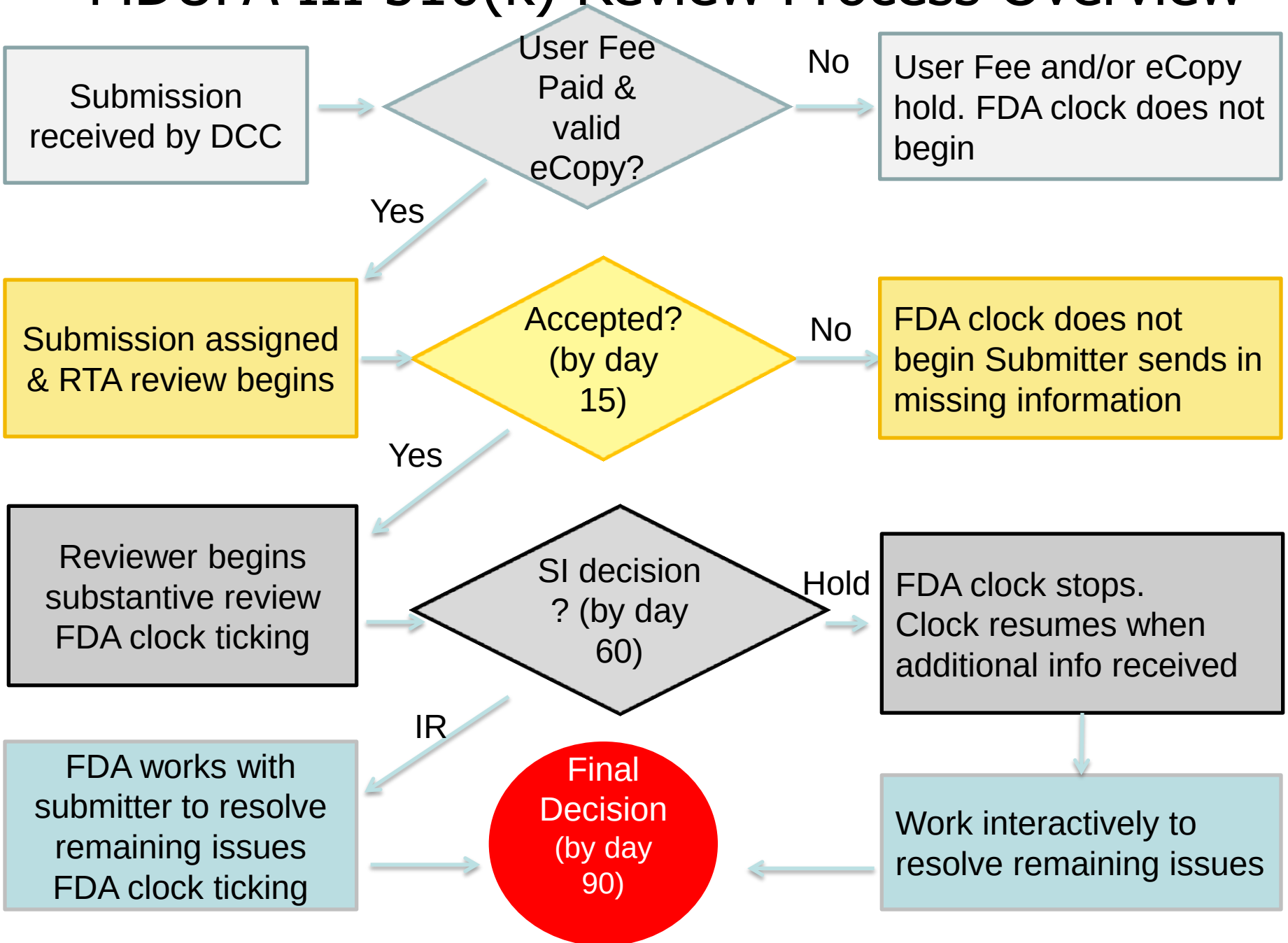
Outline

- MDUFA III Review Process Overview
- 510(k) Refuse to Accept Guidance
  - Policy Overview
  - Tips & Best Practices
- Evaluating Substantial Equivalence Guidance
  - Modified Flowchart
  - New terminology
  - “Split Predicate”
  - 510(k) Summary
- Risk/ Benefit Draft Guidance

MDUFA III 510(k) Review Process Overview



510(k) Review Phases & Milestones

- **Acceptance Review**
  - **Accept/Reject Decision by Day 15**

- **Substantive Review**
  - **Substantive Interaction (SI) decision by Day 60**

- **Finalize Review After SI**
- **MDUFA (final) decision by Day 90**
  - **Missed MDUFA communication (MMD) as needed**

510(k) Timeframes

- Under the Medical Device User Fee Amendments (MDUFA III), FDA is subject to the following performance goals:

	FY13	FY14	FY15	FY16	FY17
Substantive Interaction	65% in 60 days	75% in 60 days	85% in 60 days	95% in 60 days	95% in 60 days
Final SE/NSE Decision	91% in 90 days	93% in 90 days	95% in 90 days	95% in 90 days	95% in 90 days
Average Total Time	135 days	135 days	130 days	130 days	124 days

Average Total Time = FDA Days + Industry Days

Refuse to Accept Policy for 510(k)

- Improve submission quality
- Enhance review efficiency

510(k) Refuse to Accept

- Refuse to Accept Policy for 510(k)s guidance document
  - Outlines policy & timelines
  - Includes traditional, special, and abbreviated checklists
- Went into effect December 2012
- Steady improvement in submission quality and rate of acceptance since implementation

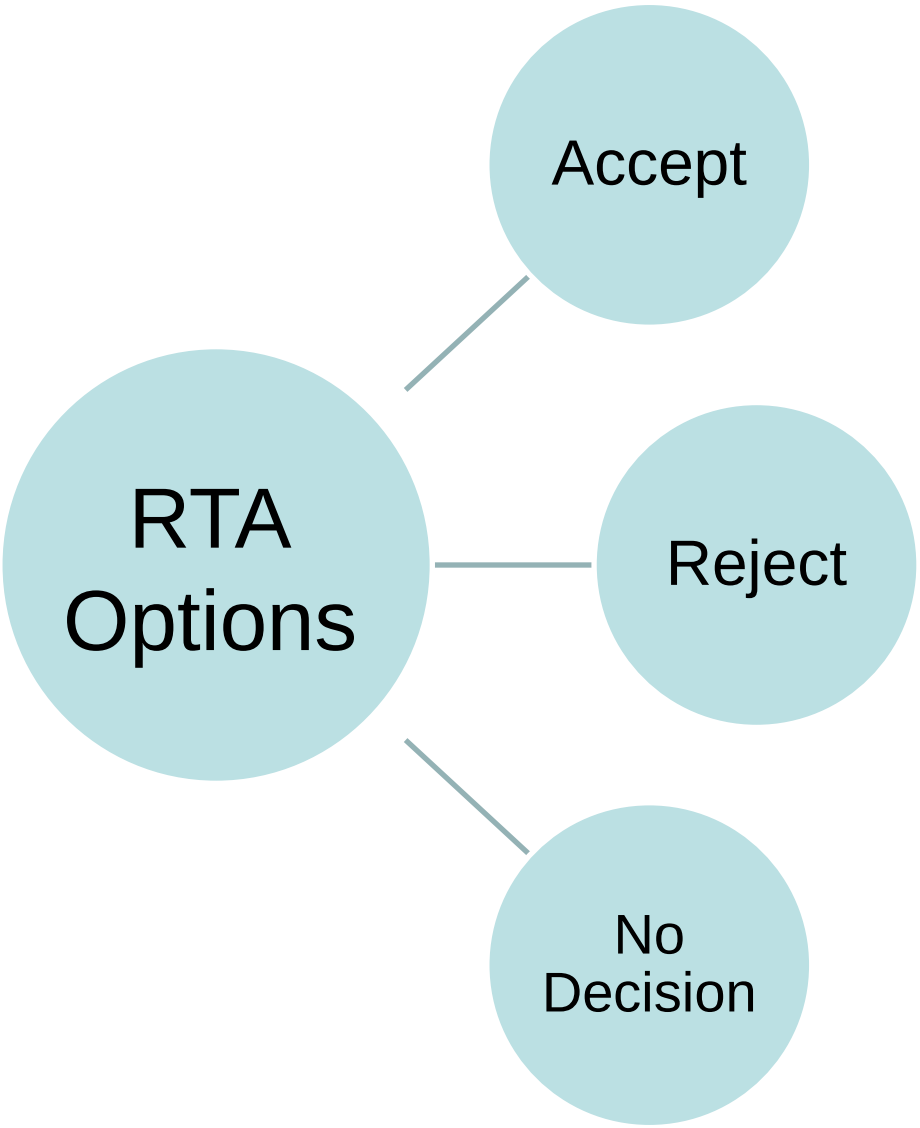
RTA Policy Highlights for Industry

- Checklist available to industry
  - Convert the checklists in the back of the guidance to Word document OR
  - Ask a reviewer or 510(k) staff for a blank PDF fillable checklist
- RTA status notification by day 16 via email
- 180 days to respond to RTA
- Complete response sent to DCC, not reviewer
- RTA review time counts towards SI day 60 goal
- No monetary penalty
  - User Fee and Refunds for Premarket Notification Submissions guidance document
- Conversion from Special to Traditional can happen at any point, including RTA window

Using the Checklists

- RTA criteria: present or not present
  - *Present*: item wholly provided OR rationale provided for omission or alternative
  - *Not Present*: item not provided (either wholly or partially) AND rationale not provided for alternative/omission
  - Not an evaluation of adequacy

- Comments:
  - Not needed for every “not present” criteria
  - Should be included to clarify what is missing (e.g., guidance partially followed)



- All checklist criteria are present
- Begin Substantive Review, but can ask for RTA info
- No effect on clock
- Notification to submitter

- One or more missing criteria
- Clock stops, resets to Day 0
- Notification to submitter w/ checklist

- Very rare occurrence
- Day 16: notification sent to submitter
- Begin Substantive Review, but can ask for RTA info
- No effect on clock

What Happens if Rejected?

- Email sent to submitter
  - Reviewer completed checklist is provided
  - Lead Reviewer identified
- Submitter has 180 days to respond to RTA
  - Response should address all missing criteria; no piecemeal response & no need to resend entire submission
    - FDA Clock resets to Day 0 when DCC receives response
  - Submitter has option to withdraw the file and request a refund
  - File closed on day 181 due to lack of response
- Reviewer conducts RTA review again with add'l info

Tips & Best Practices

- Make a good first impression
  - Be organized
    - Page numbers, headings, table of contents
    - Hyperlinks/bookmarks within eCopy are very helpful
    - Ensure eCopy text and figures are all legible and clear
  - Avoid data dump
    - Follow the order of the checklist
    - Provided info should have a purpose
      - Too much information can delay the review
  - Proofread everything
    - Ensure consistency throughout submission
      - (e.g., IFU consistency with labeling, device name consistency)
    - Tell the story of equivalence

Tips & Best Practices cont'd

- Include the checklist in the submission and indicate page numbers for where each respective criterion is addressed
- Address each checklist criterion fully
  - Be sure to include a rationale for alternative approaches or omissions
  - Don't allow the reviewer to make any assumptions about whether a criterion is applicable or not
- Make sure contact information is correct
- Contact reviewer for clarification after RTA, if needed
- Contact 510(k) Staff immediately if…
  - You don't receive an RTA status email by day 16
    - First check your "junk" folder
  - If you disagree with the "not accepted" decision

RTA's Most Wanted

- #28 SHELF LIFE: Submission includes summary of methods used to establish that device performance is not adversely affected by aging or includes a rationale for why the storage conditions are not expected to affect device safety or effectiveness.
- #9: ADMINISTRATIVE: submission identifies prior submission for the same device for which FDA provided feedback…or states that there were no prior submissions for the subject device.
- #36: PERFORMANCE DATA: Full test report is provided for each completed test. A full test report includes…an explanation of how the data generated from the test supports a finding of substantial equivalence.
- #4a: ADMINISTRATIVE: submission contains all elements of 510(k) Summary
- #17a: LABELING: Indications for use are stated in the labeling and are identical to Indications for Use form and 510k Summary

Evaluating Substantial Equivalence in Premarket Notifications [510(k)] Guidance

Evaluating Substantial Equivalence in Premarket Notifications [510(k)] Guidance

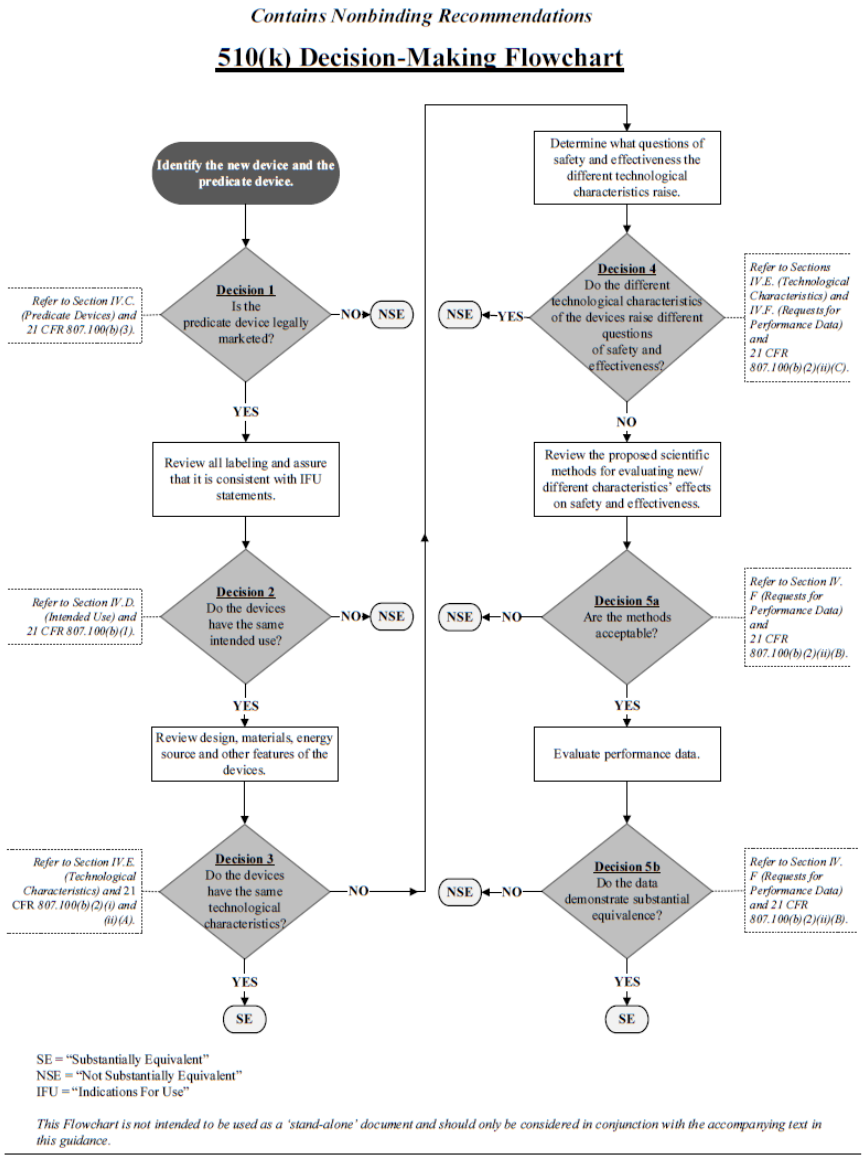
- The final guidance issued on July 28, 2014
  - Replaces only K86-3 Blue Book Memorandum
- Describes FDA's current review practices for 510(k) submissions by describing the regulatory framework, policies and underlying practices
- Does not address the Special and Abbreviated 510(k) programs

  NOTE: These sections will be finalized separately. Until then, the recommendations for Special and Abbreviated 510(k)s contained in the "New 510(k) Paradigm" guidance remain in effect for these types

Updates and Changes

- A revision of the 510(k) Decision Flowchart
- New terms with definitions
- Clarification on “Split Predicate”
- Discussion on Intended Use and Indications for Use
- Explanation of 510(k) Summary content

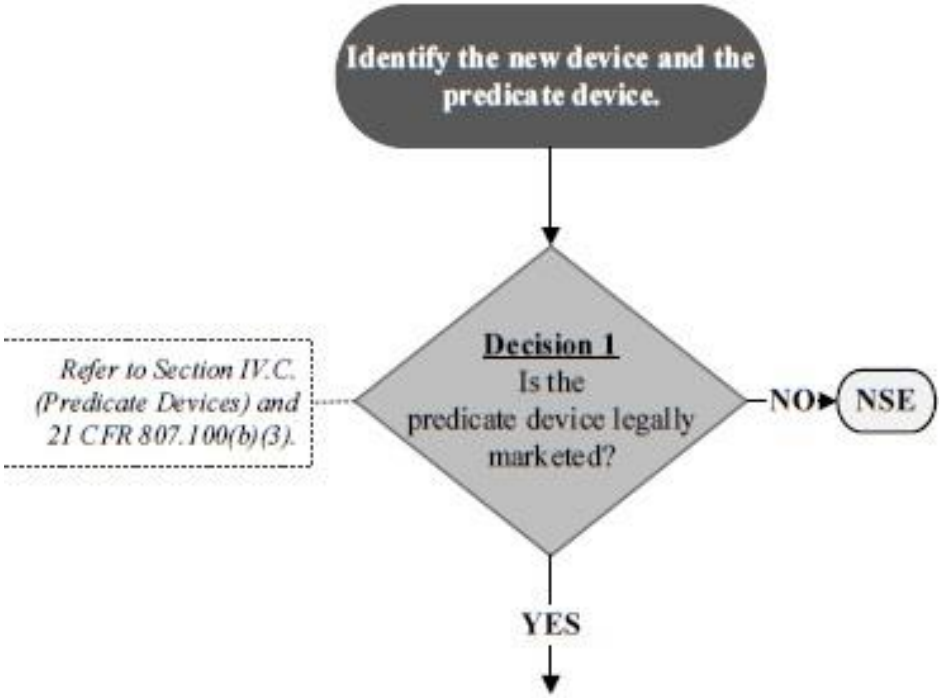
The Modified 510(k) Flowchart



- Available in Appendix A of guidance
- Updated for visual clarity & to incorporate statutory language
- Flowchart not intended to be used as a stand-alone document
- Decision questions are answered in order
- Walk through with 1 predicate at a time

Decision 1

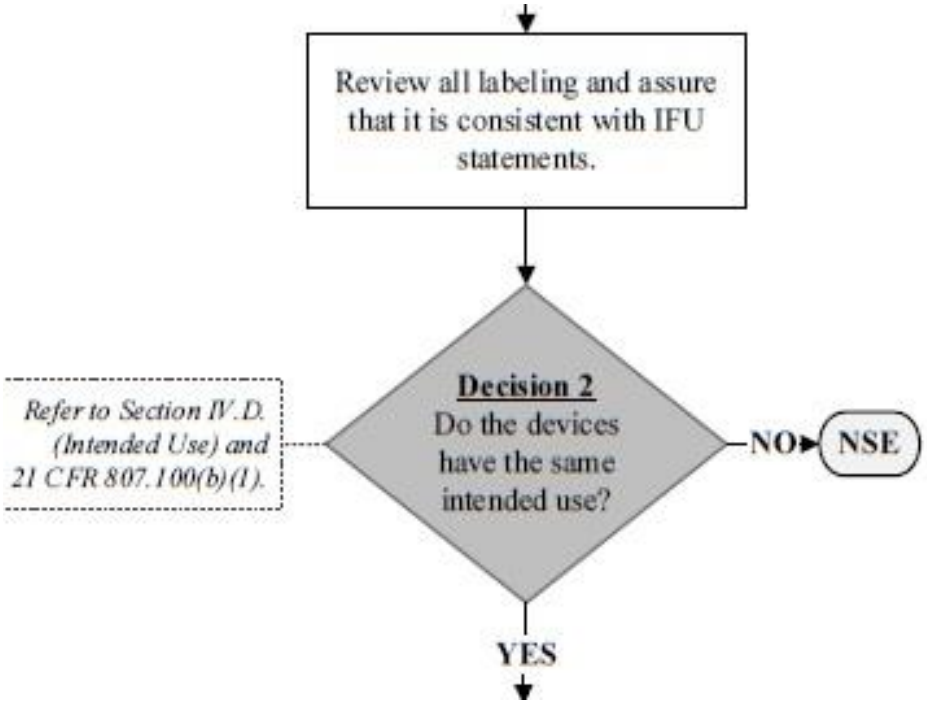
- A “legally marketed predicate” is one that either:
  - Was cleared in a 510(k)
  - Is a preamendments device
  - Is exempt from 510(k)
  - Was down-classified from Class III to II or I
  - Was granted in a de novo
- Devices that are the subject of a recall or are no longer marketed are still considered legally marketed predicates



Decision 2

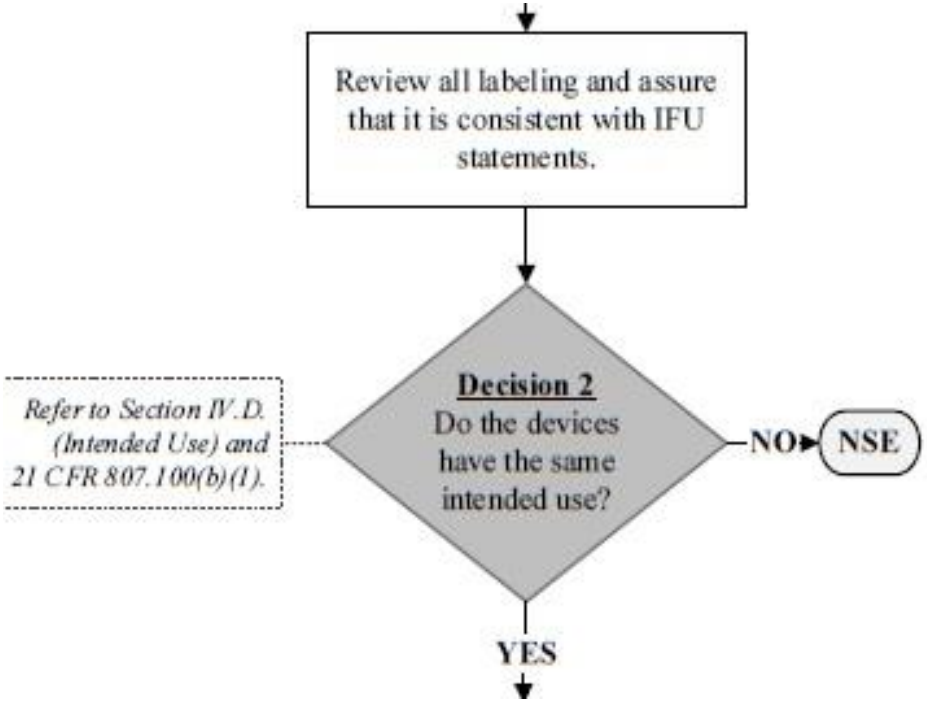
- **Intended Use** means the general purpose of the device or its function, and encompasses the indications for use.

- **Indications for Use (IFU)** describes the disease or condition the device will diagnose, treat, prevent, cure, or mitigate, including a description of the patient population for which the device is intended.



Decision 2 cont'd

- FDA evaluates the IFU statement and labeling when determining the intended use
- If the instructions for use in the labeling are inconsistent with the IFU, you may have grounds for a new intended use
- Refer to the General to Specific guidance for more info on intended use



Example (Intended Use)

- A new device's instructions for use describes general surgery use in a body cavity
- The predicate is used only to treat external injuries

- A comparison may not be adequate due to risk of infection
- An independent infection risk assessment of the predicate was not evaluated or was significantly less concerning during the predicate review

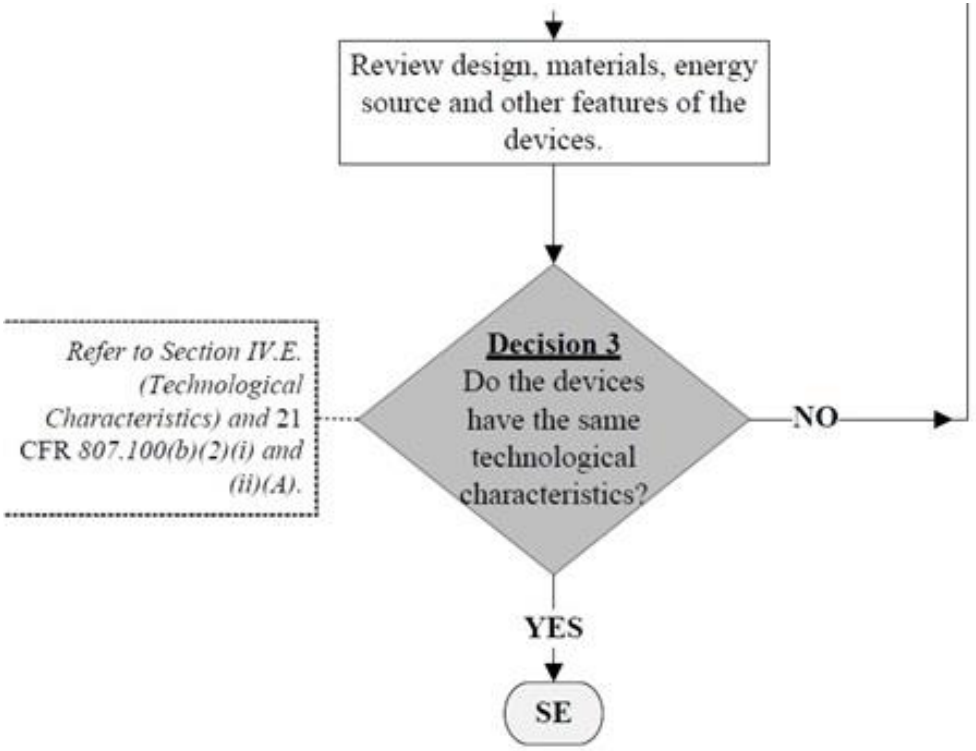
- New device may constitute a new intended use
- PMA (or alternative submission type), or if appropriate, a *De Novo* request is required

Discussion on Intended Use and Indication For Use (IFU)

- Examples of when a new Indication for Use may result in a new Intended Use
  - A change from a function/performance indications to a treatment or aesthetic indication
  - A change from a diagnostic indication to a screening indication, or visa versa;
  - A change in the anatomical structure of use;
  - A change in the patient population (e.g. adult versus pediatric)
  - A change in the clinical context or setting (e.g. hospital versus home use)

Decision 3

- Answering yes implies the descriptive characteristics are precise enough to ensure equivalence
- The descriptive characteristics may include brief summary-level analyses (e.g. engineering analyses) to show that the technological characteristics are the same
- Finding a device SE based on device description alone may be rare

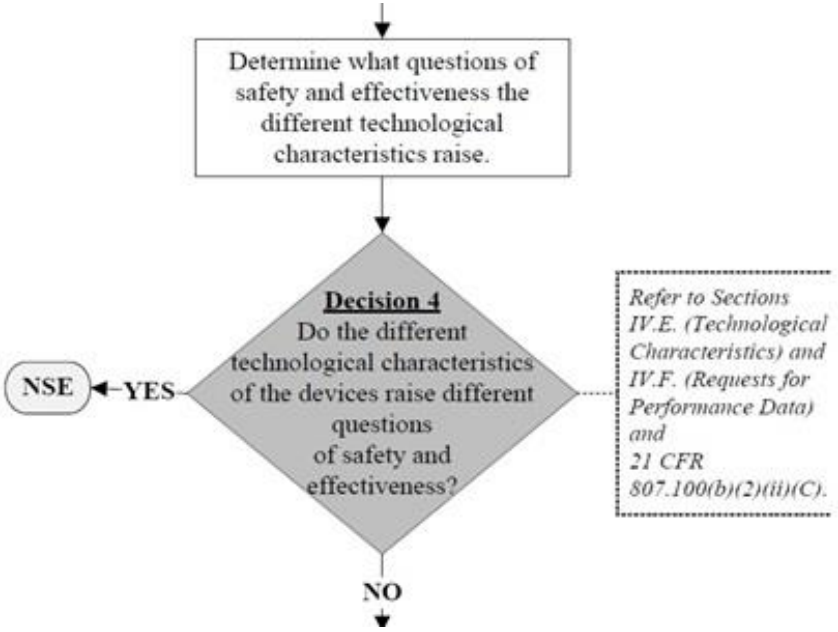


Example (Decision 3)

- A manufacturer seeks clearance for a bone screw that is larger than what valid predicates offer
  - A basic engineering analysis and clinical rationale was provided showing that the new screw does not introduce a new worst case and a performance evaluation is not needed
  - It can be determined that the technological characteristics are the same -> SE
- A different manufacturer seeks clearance for a bone screw that is smaller than what valid predicates offer
  - The provided descriptive and engineering analyses were not sufficient to establish equivalent technological characteristics
  - Move on to Decision 4 (Do the technological differences raise different questions of safety and effectiveness?)

Decision 4

- The old flowchart asked if new characteristics raised “new types of safety or effectiveness questions?”
  - New language matches the regulation
- A “different question of safety or effectiveness” is a question raised by the technological characteristics of the new device that was not applicable to the predicate device, and poses a unique safety or effectiveness concern for the new device.
- FDA is responsible for identifying the “different question”
- It only takes 1” different question”



Example (Decision 4)

- A new device externally applies vacuum around the neck to move soft tissue and “open” the airway

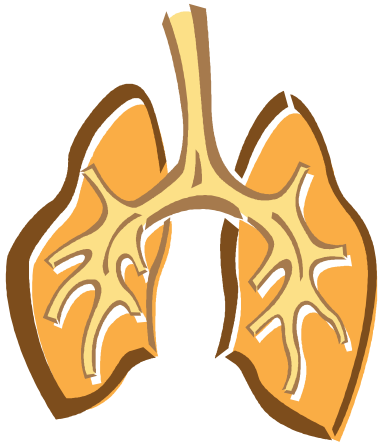
- The predicate device (Decision 1) is a tube inserted into the patient’s pharynx through the mouth to provide an airway by mechanically moving soft tissue

- The intended use is the same (Decision 2)
- There are different technological characteristics (Decision 3)

- The new device exerts continuous pressure on all soft tissue in neck and the predicate does not

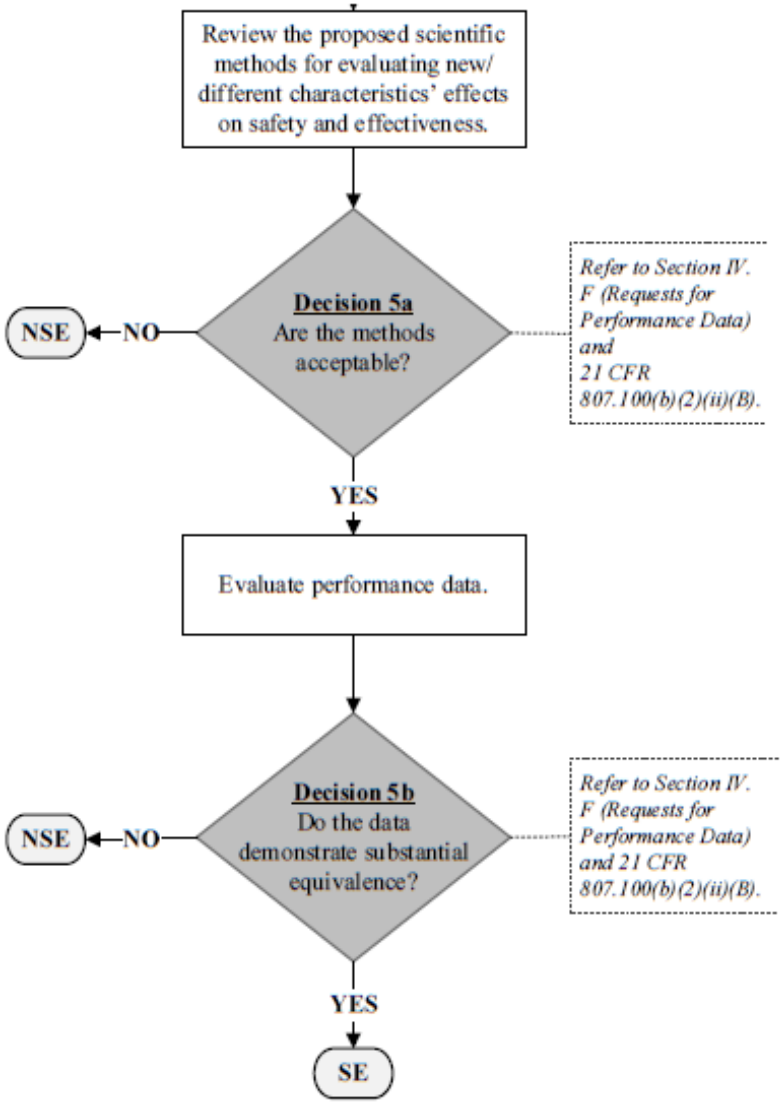
- The new device raises concerns with potential adverse events associated with the stimulation of nerve structures in the neck and the predicate does not raise this type of question

- Because these types of questions were not necessary to take into account for the predicate device, the new device would be found NSE



Decisions 5a and 5b

- If there are no different questions of S&E, can data be used to evaluate the differences?
  - Includes reference devices
- 5a & 5b (i.e., Performance Based issues) are most common reason for NSE decisions



New Terminology: Primary Predicate

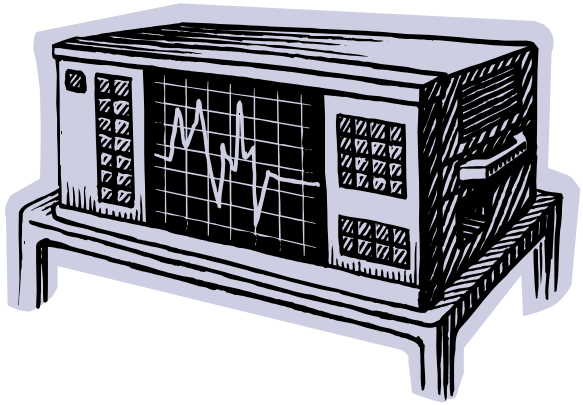
- ***Primary Predicate –*** the identified predicate with indications and technology most similar to the subject device when multiple predicates are identified
  - Sponsor should suggest the primary predicate; however, final decision is up to reviewer
  - Identifying a Primary Predicate can facilitate a timely review and well-supported decision
    - identify the minimum number of predicates to demonstrate SE
    - help track predicate lineage and technology changes
  - Must be able to address Decision points 1-4 with one primary predicate

Example (Multiple Predicates)

- New hemodialysis catheter with an extension piece similar to legally marketed (Decision 1) predicate A and a tip similar to legally marketed predicate B
  - Both predicates have same intended use (Decision 2)
  - The technological characteristics of the new device are not the same as the predicates (Decision 3)
  - The technological characteristics do not raise different questions of safety and effectiveness in regard to the predicates (Decision 4)
- Either predicate can serve as primary predicate

Example (Multiple Predicates)

- A multi-parameter monitor that combines different technologies to measure various patient parameter information
- Predicates exist for each technology and parameter display and are classified under different regulations
- Assuming the monitoring of each individual parameter does not interfere with the others, the device can be found SE
- A primary predicate that best suits the subject device should be identified



New Terminology: Reference Device

- ***Reference Device*** – a legally marketed device intended to provide scientific information to support safety and effectiveness.
  - Reference devices may be used to support scientific methodology or standard reference values at Decision Point 5a
  - Reference device is NOT a predicate and cannot be used to support decision points 1-4 on the Flowchart.
  - Reference devices are not meant to alter data requests
  - Reviewer still has authority to decide what data is necessary

Example (Reference Predicate)

- Total knee implant with new coating X
  - Other total knee implants with coatings A, B, and C are legally marketed and have the same intended use (Decisions 1 and 2)
  - A total hip implant is cleared with coating X
- New implant does not have same technological characteristics due to a different coating than other knee implants(Decision 3), but do not raise different questions of safety and effectiveness (Decision 4).
- Predicate knee implant with coating A has served as a comparator for Decisions 1-4 in the Flowchart and can be the Primary Predicate
- Total hip implant with coating X can be the Reference Predicate for support of appropriate scientific methods for characterization (Decision 5)
- The review team decides the extent to which the data from the hip implant can be used to support the subject device

Split Predicate

- Refers to demonstrating the 510(k) decision making process by combining the intended use of one device with technological characteristics of another
- The guidance clarifies “The use of Split Predicate is inconsistent with the 510(k) Regulatory Standard”
- To obtain SE, FDA should be able to walk down the flowchart (at least Decisions 1-4) using the primary predicate
  - FDA may use one or more additional devices proposed by the manufacturer in certain instances to help support substantial equivalence

Predicates

- Every predicate should be utilized for some aspect of the comparison review
  - Sponsor should provide reason for citing each predicate
- Reviewer should remove extraneous predicates
  - If the Sponsor does not provide a unique reason for citing a specific predicate for comparison to the subject device, do not include it in the 510(k) Summary
- Valid predicates that are not identified as the primary predicate should be referenced in the 510(k) Summary (e.g. labeled as “Additional Predicates”)

510(k) Summary

- What is a 510(k) Summary?
  - It is the “book report” for how the device got cleared
- What is a 510(k) Summary for?
  - A 510(k) Summary helps companies determine what needs to be provided in future submissions

510(k) Summary

- Guidance includes additional discussion and examples on 510(k) Summary requirements and content
- Appendix B – discussion on 510(k) Summary document requirements
  - provides clarification to facilitate compliance with 510(k) Summary content requirements in 21 CFR 807.92
  - Each subpart of the regulation explained with suggested content
- Appendix C – sample of compliant 510(k) Summary
  - Intended to provide a example of the format and content expected

510(k) Summary

21 CFR 807.92

- (b) 510(k) summaries for those premarket submissions in which a determination of substantial equivalence is also based on an assessment of performance data shall contain the following information:
- (1) A brief discussion of the nonclinical tests submitted, referenced, or relied on in the premarket notification submission for a determination of substantial equivalence;
- (2) A brief discussion of the clinical tests submitted, referenced, or relied on in the premarket notification submission for a determination of substantial equivalence. This discussion shall include, where applicable, a description of the subjects upon whom the device was tested, a discussion of the safety or effectiveness data obtained from the testing, with specific reference to adverse effects and complications, and any other information from the clinical testing relevant to a determination of substantial equivalence; and
- (3) The conclusions drawn from the nonclinical and clinical tests that demonstrate that the device is as safe, as effective, and performs as well as or better than the legally marketed device identified in paragraph (a)(3) of this section.
- (c) The summary should be in a separate section of the submission, beginning on a new page and ending on a page not shared with any other section of the premarket notification submission, and should be clearly identified as a "510(k) summary."
- (d) Any other information reasonably deemed necessary by the agency.

510(k) Summary

- In Conclusion section, discourage “safe and effective” language without qualifying the comparative basis for substantial equivalence
  - Bad: “Based on a review of the information provided, the subject device was found to be safe and effective.”
  - Better: “Based on a review of the information provided, the subject device was found to have an equivalent safety and effectiveness profile compared to the predicate.”
- In Performance Data section please be sure the Sponsor appropriately cites and provides a brief description of the applicable standards and also non-standard testing

510(k) Summary

- 510(k) Summaries may not need to be as detailed as the example provided in Appendix C
- Best practice is to include every section header as provided in the example, even if the section is “N/A”
- Primary Predicate, Additional Predicates, and Reference Devices need to be provided, if applicable
  - Example:

Best practice

III. Predicate Device:

Brand Z Endoscopic Plication System, KXXXXXX

This predicate has not been subject to a design-related recall.[40]

No additional predicates or reference devices were used in this submission.

[40] On July 9, 2012, section 605 of FDASIA (Pub. L. 112-144) added section 518A to the FD&C Act, which directs FDA to establish a program to routinely and systematically assess information regarding device recalls, and to use that information to proactively identify strategies for mitigating health risks presented by defective or unsafe devices. FDA believes that one way to carry out this directive is to provide greater transparency on recalled devices. Identifying whether a predicate was recalled is optional, but doing so would help the Agency achieve this FDASIA directive.

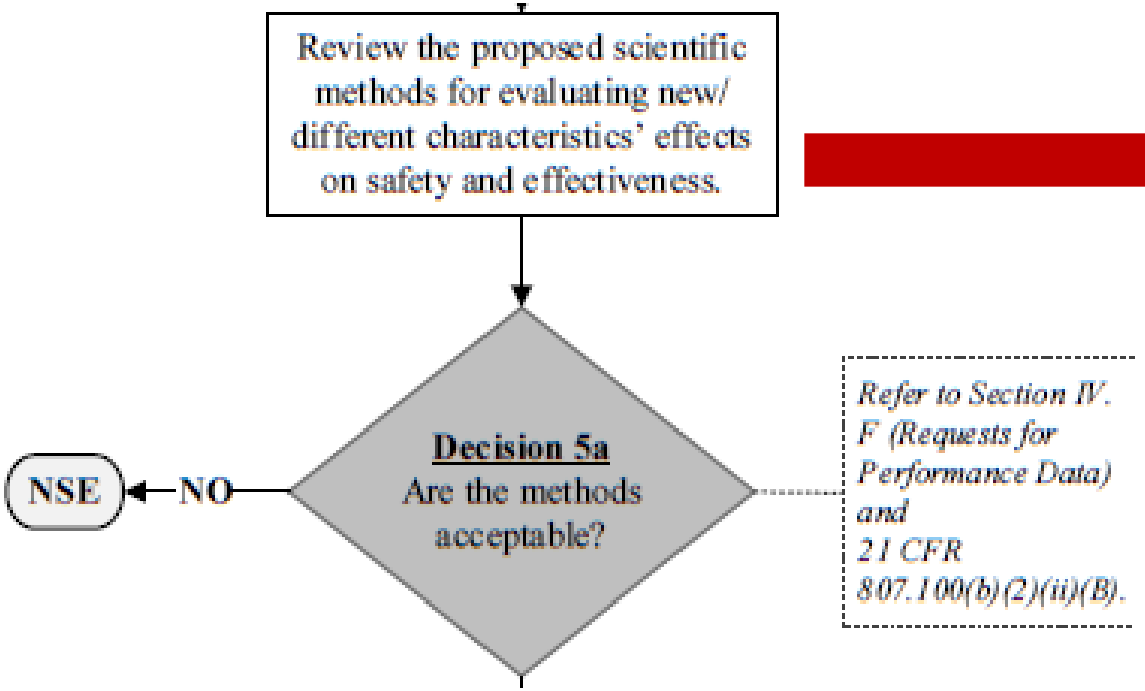
Benefit- Risk Factors to Consider When Determining Substantial Equivalence in Premarket Notifications [510(k)] With Different Technological Characteristics

DRAFT Guidance

Benefit/Risk Draft Guidance

- DRAFT guidance issued July 15, 2014
- Intended to offer clarification on when and how to consider benefit/risk with respect to evaluating device safety and effectiveness
  - Does not alter the regulatory framework or intent of 510(k) Program
  - Risk/Benefit draft guidance does not address questions 1-4 in the 510(k) Decision Making Flowchart
  - Offer clarity in factors that FDA considers when making substantial equivalence determinations when there are different technological characteristics between the new device and the predicate device that do not raise different questions of safety and effectiveness

Role of Benefit/Risk Analysis in 510(k)



- FDA evaluates the differences to determine whether the new device is "as safe and effective" as the predicate.
- FDA determines the safety and effectiveness of a device by weighing probable benefit against probable risk

NOTE: Risk/Benefit levels do not always have to be equivalent to reach SE:

Decreased Benefit & Decreased Risk OR Increased Benefit & Increased Risk: Reviewers weigh the degree of change in benefit against the degree of change in risk. May reach SE despite decreased benefit or increased risk.

Assessment of Benefits & Risks

- Benefits
  - Type: directly measured clinical benefits (e.g., survival, improvement) or indirectly measured benefits (e.g., impact to public health)
  - Magnitude & Probability: the extent to which benefit is achieved & likelihood of achieving benefit within user population
  - Duration of Effect: how long will the benefit last and how is it achieved (single use vs. ongoing treatment).
- Risks
  - Severity & Type: serious vs. non-serious adverse events or procedure related complications
  - Probability: likelihood of occurrence and proportion of affected population
  - Duration of Harm: temporary, minor, reversible, permanent
  - Risks for diagnostics: false positive or false negative impacts

Add'l 510(k) Light Reading

- Device Advice: How to Prepare a 510(k) (FDA website)
  - Format for Traditional and Abbreviated 510(k)s guidance
- User Fee and Refunds for 510(k) guidance
- eCopy Program for Medical Device Submissions guidance
- FDA and Industry Actions on 510(k) Submissions guidance
- The New 510(k) Paradigm- Alternate Approaches to Demonstrating Substantial Equivalence guidance
- Types of Communication During the Review of Medical Device Submissions guidance

Questions?